

DRUGDEX-EV 0620

MICROMEDEX

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Database updated March 2017

CHLORDIAZEPOXIDE/AMITRIPTYLINE HYDROCHLORIDE

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0.0] Overview

1] Class

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

Tricyclic Antidepressant/Benzodiazepine Combination

2] Dosing Information

a) Adult

1) Mixed anxiety and [depressive disorder](#)

a) 10 mg [chlordiazepoxide](#)/25 mg [amitriptyline](#) ORALLY 3 to 4 times a day

b) Pediatric

1) [safety and effectiveness in children have not been established](#) [15]

3] Contraindications

a) Coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (eg, hyperpyretic crisis, severe convulsions, death) [17]

b) Hypersensitivity to benzodiazepines or tricyclic antidepressants [17]

c) Use during acute recovery period after [myocardial infarction](#) (MI)[17]

4] Serious Adverse Effects

a) [Cardiac dysrhythmia](#)

b) Decreased liver function

c) Depression, Worsening

d) [Electrocardiogram](#) abnormal

e) [Myelosuppression](#)

f) Suicidal thoughts

g) Suicide

5) Clinical Applications

a) FDA Approved Indications

1) Mixed anxiety and [depressive disorder](#)

1.0] Dosing Information

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1.1] Drug Properties

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

B) Physicochemical Properties

1) Molecular Weight

a) [Amitriptyline](#) hydrochloride: 313.87; [chlordiazepoxide](#): 299.76 [18]

2) Solubility

a) [Amitriptyline](#) is freely soluble in water; [chlordiazepoxide](#) is insoluble in water [18]

1.2] Storage and Stability

A) Oral route

1) Tablet

a) Store at 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from moisture [18].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Important Note

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

1.3.1.B] Oral route

1.3.1.B.1] Mixed anxiety and depressive disorder

a) Optimum dosage varies with the severity of the symptoms and response of the individual patient. The manufacturer recommends that the larger portion of the daily dose be given at bedtime. In some patients, a single dose at bedtime may be sufficient [14].

b) The initial recommended dose is 30 to 40 milligrams (mg) [chlordiazepoxide](#)/75 to 100 mg [amitriptyline](#) (3 to 4 tablets) daily in divided doses. This dose may be increased to 60 mg [chlordiazepoxide](#)/150 mg [amitriptyline](#) per day (6 tablets), if necessary. Some patients will respond to smaller doses and can be maintained on 2 tablets/day [14].

1.3.4] Dosage in Geriatric Patients

A) A reduced dose is suggested in the elderly to prevent the development of ataxia, oversedation, confusion or anticholinergic effects [14].

1.3.6] Dosage in Other Disease States**A) CYP2D6 Phenotypes**

1) Ultrarapid metabolizers: Avoid use due to potential lack of efficacy; if use is necessary, increase starting dose [16]

2) Extensive metabolizers: Dose adjustment not necessary [16]

3) Intermediate metabolizers: Reduce starting dose by 25% [16]

4) Poor metabolizers: Avoid use due to increased risk for adverse effects; if use is necessary, reduce starting dose by 50% [16]

B) CYP2C19 Phenotypes

1) Ultrarapid metabolizers: Consider alternative drug not metabolized by CYP2C19 [16]

2) Extensive metabolizers: Dose adjustment not necessary [16]

3) Intermediate metabolizers: Dose adjustment not necessary [16]

4) Poor metabolizers: Reduce starting dose by 50% [16]

2.0] Pharmacokinetics[Onset and Duration](#)[Drug Concentration Levels](#)[ADME](#)**2.1] Onset and Duration****A) Onset****1) Initial Response**

a) [AMITRIPTYLINE](#): Anxiety/depression, oral: 7 to 21 days [1064]

2.2] Drug Concentration Levels

A) Time to Peak Concentration

1) **CHLORDIAZEPOXIDE**: Oral: 30 minutes to 12 hours [1065][1066][1067]

a) One to 3 days are required to reach steady-state concentrations [1065]. Some subjects demonstrate a peak blood level in 4 hours [1066].

b) Following single oral doses of 20 mg, plasma levels rapidly rise to a peak of approximately 1 mcg/mL at 2 to 6 hours and then decrease according to first-order kinetics [1067].

2) **AMITRIPTYLINE**: Oral: 2 to 12 hours [1068]

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

1) **CHLORDIAZEPOXIDE**: Nearly completely absorbed after a single oral dose [1065].

2) **AMITRIPTYLINE**: Tricyclic antidepressants are absorbed completely, but systemic availability is reduced by pronounced hepatic first-pass elimination [1069].

3) Following oral administration, **amitriptyline** is rapidly absorbed [1070][1071][1072].

4) Once-daily doses taken in the morning may result in higher blood levels than the same dose taken in the evening, according to a study in 10 subjects [60].

2.3.2] Distribution**A) Distribution Sites****1) Protein Binding**

a) **CHLORDIAZEPOXIDE**: 90% to 98% [1073]

1) Protein binding may be decreased in alcoholic liver disease, producing higher peak serum concentrations of free drug than normal. Single doses of drug may have to be smaller to achieve the same therapeutic effect. However, the average free serum concentration of drug during sustained therapy is normal. Thus, chronically decreased protein binding does not usually require any change of dosage schedule during chronic administration, but severe liver disease may dictate dosage reduction because of impaired drug metabolism.

b) **AMITRIPTYLINE**: 90% to 95% [1074]

B) Distribution Kinetics**1) Volume of Distribution**

a) **CHLORDIAZEPOXIDE**: 3.3 L [1067]

1)) This Vd followed a single 20-mg intravenous dose and approximated plasma volume and a total volume of distribution of 25% of body weight [1067].

2.3.3] Metabolism

A)) Metabolites

1)) CHLORDIAZEPOXIDE

a)) Desmethylchlordiazepoxide (active) [1075]

b)) Demoxepam (active) [1075]

1)) Both metabolites have nearly the psychopharmacologic activity of the parent compound. Thus, multiple dosing results in accumulation of the drug and its active metabolites producing a cumulative clinical effect [1075]. Both metabolites have marked pharmacologic activity in animals [1076].

2)) Antianxiety effects in 15 subjects with moderate to severe anxiety correlated with plasma levels of desmethylchlordiazepoxide and demoxepam rather than with chlordiazepoxide [1077].

3)) N-desmethylchlordiazepoxide is reported to exist in a 0.22 to 0.28 ratio to the parent versus a 0.3 to 0.34 ratio for demoxepam [1078].

2)) AMITRIPTYLINE

a)) Nortriptyline (active) (Santagostino et al, 1974)[1079][1080][1072]

1)) Nortriptyline retains sedative and antireserpine properties similar to amitriptyline [1076][1070], and is used clinically. Nortriptyline is reported to exist in a ratio of 0.35 to 1.0 to the parent compound in the plasma [1076].

2)) In a comparison of the amount of nortriptyline formed through metabolism of amitriptyline given by either oral or intramuscular routes, area under the concentration-time curve (AUC) increased with intramuscular dosing and the nortriptyline peak occurred earlier with oral dosing [1081]. Six healthy subjects received either 50 mg orally (PO) or 25 mg intramuscularly (IM), then were crossed-over after a 2-week period. The ratio of AUC after PO dosing to IM dosing ranged from 0.69 to 1.13 (mean 0.95). The nortriptyline peak occurred at 24 to 48 hours after intramuscular dosing, and at 8 to 24 hours after oral dosing. The earlier peak after PO dosing was concluded to result from the first-pass effect.

3)) In another trial examining the extent of demethylation occurring after oral versus intramuscular dosing of amitriptyline, the total amount of nortriptyline formed was approximately equivalent after either route [1082].

b)) 10-hydroxy derivatives (active) (Santagostino et al, 1974)[1079][1080][1072]

c) Conjugated derivatives (inactive) (Santagostino et al, 1974)[1079][1080][1072]

1)) Other metabolites include the 10-hydroxy derivative of nortriptyline and the glucuronated derivatives of both compounds (Santagostino et al, 1974)[1079][1080].

2)) In a comparison of amitriptyline metabolites in 10 alcoholic versus "nonalcoholic" depressive patients, the mean nortriptyline plasma level was significantly lower in the alcoholic patients, as was its urinary excretion, while plasma levels of conjugated hydroxyamitriptyline and its urinary excretion were significantly higher in alcoholic patients. Thus, alcoholics appear to demethylate less amitriptyline and hydroxylate and conjugate more. This is of significance because conjugate metabolites are inactive whereas demethylated and hydroxylated metabolites may be active [1083].

3)) Increased concentrations of conjugated amitriptyline metabolites were found in 7 patients with chronic renal failure undergoing hemodialysis, suggesting that these metabolites may be responsible for the increased incidence of adverse peripheral effects in these patients [1084].

2.3.4] Excretion

A)) Kidney

1)) Renal Excretion (%)

a)) 18% free drug [1079]

1)) The remainder of the drug is excreted as the N-oxide, 10-hydroxy derivatives of nortriptyline and nortriptyline's 10-hydroxy derivatives (Santagostino et al, 1974) [1079][1080].

B)) Other

1)) OTHER EXCRETION

a)) SALIVA

1)) CHLORDIAZEPOXIDE

a)) Saliva and plasma concentrations were highly correlated ($r=0.95$) based on data obtained in 3 subjects. Saliva levels were found to be equal to the concentration of unbound drug in the plasma [1094].

2.3.5] Elimination Half-life

A)) Parent Compound

1)) ELIMINATION HALF-LIFE

a)) CHLORDIAZEPOXIDE

1j) 6.6 to 48 hours (Prod Info Librium(R), 1995)[1067]

a) The elderly and those with severe hepatic diseases may have longer half-lives because of slower rates of metabolism, while smokers may degrade the drug more rapidly.

b) When the disposition of a single 50-mg intravenous dose was compared in 14 normal subjects and 11 patients with biopsy-proven cirrhosis, the half-life was significantly prolonged in patients with cirrhosis (43.9 +/- 8.7 hr) compared to normal subjects (10.0 +/-0.9 hr) [1095].

b) AMITRIPTYLINE

1j) 10 to 50 hours, administered alone [1068].

a) After 1 week of therapy, 9 to 25 hours (average, 15 hours) [1096][1070]

b) When diazepam and amitriptyline were administered concurrently in 5 patients, an increase in amitriptyline half-life and serum plasma concentration was documented [1068]. A decrease in plasma clearance was also noted. The mechanism by which this interaction occurs is not clear but may be attributed to a change in volume of distribution. The clinical significance of this interaction is questionable. Large increases or decreases in plasma concentrations of a drug when another is simultaneously administered is not necessarily followed by corresponding clinical changes [1097].

B) Metabolites

1j) Demoxepam, 14 to 95 hours [1067].

2j) Desmethylchlordiazepoxide, the major metabolite, appeared in blood of cirrhotic patients less rapidly than in normal subjects [1095].

2.3.6] Extracorporeal Elimination

A) Hemodialysis

1j)Dialyzable: No[1085][1086]

a) **Hemodialysis** removed only insignificant amounts (undetectable by assay) of chlordiazepoxide in overdose [1085][1086].

b) No [1087][1088][1089][1090][1091][1092]

1j) Hemodialysis does not remove significant amounts of the tricyclic antidepressants and does not appear to alter the plasma elimination curve [1087][1088][1089][1090][1091][1092].

B) Peritoneal

1j) Dialyzable: No[1093][1087][1088][1089][1090][1091][1092]

a) **Peritoneal dialysis** does not remove significant amounts of the tricyclic antidepressants and does not appear to alter the plasma elimination curve [1093][1087][1088][1089][1090][1091][1092].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.0.A] Black Box WARNING

Oral (Tablet)

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 chlordiazepoxide and amitriptyline 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. Chlordiazepoxide and amitriptyline is not approved for use in pediatric patients [17].

3.1] Contraindications

A) Coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (eg, hyperpyretic crisis, severe convulsions, death) [17]

B) Hypersensitivity to benzodiazepines or tricyclic antidepressants [17]

C) Use during acute recovery period after [myocardial infarction](#) (MI)[17]

3.2] Precautions

A) Black box warning: Increased risk of [suicidal ideation](#) and behavior or worsening depression, particularly in children, adolescents, and young adults with [major depressive disorder](#) and during the first few months of therapy or following changes in dosage; monitoring and possible discontinuation recommended [17]

B) Beers Criteria: Avoid use in elderly due to increased benzodiazepine sensitivity and highly anticholinergic and sedating effects, especially patients with a history of falls or fractures (unless safer alternatives are not available), [dementia](#), cognitive impairment, patients with or at high risk of [delirium](#), patients at risk of syncope, and men with lower urinary tract symptoms or [benign prostatic hyperplasia](#). Ataxia, bradycardia, syncope, orthostatic hypotension, falls, impaired psychomotor function, other adverse CNS effects, or worsening of current disease states may occur. Caution is advised and monitoring recommended, if used, as SIADH or [hyponatremia](#) may occur or worsen [1].

- C) Cardiovascular: [Sinus tachycardia](#), conduction time prolongation, [arrhythmias](#), [myocardial infarction](#) (MI), and [stroke](#) may occur; monitoring recommended in patients with [cardiovascular disorders](#) [17].
- D) Concomitant use: Use of alcohol or other CNS depressants may cause oversedation [17].
- E) Endocrine and Metabolic: Patients with [hyperthyroidism](#) or concurrent use of thyroid medications; monitoring recommended [17].
- F) Hepatic: Use caution in patients with [hepatic impairment](#) [17].
- G) Neurologic: Concurrent use with [electroconvulsive therapy](#) (ECT) not recommended except in patients for whom it is essential [17].
- H) Neurologic: Use caution in patients with history of seizure disorder [17].
- I) Ophthalmic: Angle-closure attack may occur in patients with anatomically narrow angles without patent [iridectomy](#) [17].
- J) Pregnancy: Use during pregnancy not recommended [17].
- K) Psychiatric: Precipitation of a mixed/[manic episode](#) may occur in patients with [bipolar disorder](#) [17].
- L) Renal: Use caution in patients with [renal impairment](#) or a history of urinary retention [17].
- M) Special populations: Avoid use in ultrarapid CYP2D6 metabolizers due to potential lack of efficacy; if used, increase starting dose and therapeutic drug monitoring recommended [16].
- N) Special populations: Reduce starting dose and monitoring recommended in intermediate CYP2D6 metabolizers [16].
- O) Special populations: Avoid use in poor CYP2D6 metabolizers due to potential adverse effects; if used, reduce starting dose and monitoring recommended [16].
- P) Special populations: Consider alternative drug therapy in ultrarapid CYP2C19 metabolizers; if used, monitoring recommended [16].
- Q) Special populations: Reduce starting dose and monitoring recommended in poor CYP2C19 metabolizers [16].
- R) Surgery: Discontinue use several days before elective surgery [17].

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Cardiac dysrhythmia

- 1) [Myocardial infarction](#), [arrhythmias](#), [heart block](#), and [tachycardia](#) have been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product. Patients with [cardiovascular disorders](#) should be watched closely when [amitriptyline/chlordiazepoxide](#) is given [18].
- 2) Following usual doses of [amitriptyline](#) administered orally or intravenously, [arrhythmias](#) have been reported to occur and include [complete heart block](#), [ventricular tachycardia](#), and [ventricular extrasystoles](#) [23][24][25]. Although elderly patients may be at a higher risk, tricyclic antidepressant-induced [cardiac arrhythmias](#) have been reported in younger patients [23]. Unexpected or sudden death associated with tricyclic antidepressant therapy may be a result of cardiac effects in the use of the drug in patients who are elderly and/or have preexisting [heart disease](#) (Moir et al, 1972 & 1973)[26].
- 3) The cardiovascular effects of [amitriptyline](#) (0.93 to 1.15 mg/kg/day) were compared with binedaline (1.85 to 2.31 mg/kg/day) in 8 healthy volunteers. Each volunteer received each medication plus placebo for 5 days, followed by 9-day washout periods. Both drugs caused significant [tachycardia](#). No other major changes in ECG or systolic time intervals were noted [27].

3.3.1.B] Cerebrovascular accident

- 1) [Stroke](#) has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

3.3.1.C] **Electrocardiogram abnormal**

1) Tricyclic antidepressants (such as [amitriptyline](#)) have been reported to cause prolongation of cardiac conduction time, [sinus tachycardia](#), and [arrhythmias](#), particularly when used at higher doses. Patients with [cardiovascular disorders](#) should be watched closely when [amitriptyline/chlordiazepoxide](#) is given [18].

2) The cardiovascular effects of [amitriptyline](#) (50 to 150 mg daily) were compared with [trazodone](#) (100 to 300 mg daily) in 20 patients with [major depressive disorders](#). [Amitriptyline](#) was shown to have the expected anticholinergic and quinidine-like effects on the ECG; [trazodone](#) lacked any significant effect [28].

3) ECG effects reported in patients who received therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc), and flattened T waves. In addition, production and suppression of atrial and [ventricular arrhythmias](#) have been reported [29].

3.3.1.D] **Hypotension**

1) Hypotension has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

2) The cardiovascular effects of [amitriptyline](#) (0.93 to 1.15 mg/kg/day) were compared with binedaline (1.85 to 2.31 mg/kg/day) in 8 healthy volunteers. Each volunteer received each medication plus placebo for 5 days, followed by 9-day washout periods. [Amitriptyline](#) caused a marked degree of postural hypotension, unlike binedaline [27].

3.3.1.E] **Malignant hypertension**

1) [Malignant hypertension](#) was reported in a 66-year-old man with [borderline hypertension](#) and migraine headache following administration of [amitriptyline](#) 50 mg daily for 6 weeks. At this time, blood pressure was 210/120 mmHg with grade IV hypertensive fundal changes. The drug was discontinued and blood pressure was controlled with [metoprolol](#). The authors suggest blood pressure monitoring during [amitriptyline](#) therapy [30].

3.3.1.F] **Myocardial infarction**

1) [Myocardial infarction](#), [arrhythmias](#), [heart block](#), and [tachycardia](#) have been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product. Patients with [cardiovascular disorders](#) should be watched closely when [amitriptyline/chlordiazepoxide](#) is given [18].

3.3.1.G] **Sudden cardiac death**

1) According to one study, the use of higher-dose tricyclic antidepressants (TCAs) was associated with an increased risk of sudden cardiac death, while lower doses did not increase this risk. In a cohort study including 481,744 persons and 1487 cases of sudden cardiac death occurring in a community setting, researchers found that compared to nonuse, the current use of TCAs was associated with a dose-related increase in the risk of sudden cardiac death. For doses lower than 100 mg ([amitriptyline](#) or its equivalent), the rate ratio was 0.97 (95% confidence interval (CI), 0.72 to 1.29), however this increased to 2.53 (95% CI, 1.04 to 6.12) for doses of 300 mg or more ($p=0.03$, test for dose response). In the entire cohort, users of TCAs in doses of 100 mg or higher ([amitriptyline](#) or its equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% CI, 1.02 to 1.95). However, TCAs taken in doses of less than 100 mg ([amitriptyline](#) or its equivalent) were not associated with an increased risk of sudden cardiac death in the

entire cohort or in any subgroups, including persons with treated [cardiovascular disease](#). Use of SSRIs was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15) [22].

3.3.1.H] Syncope

1) Syncope has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product. Patients with [cardiovascular disorders](#) should be watched closely when [amitriptyline/chlordiazepoxide](#) is given [18].

3.3.1.I] Tachycardia

1) [Myocardial infarction](#), [arrhythmias](#), [heart block](#), and [tachycardia](#) have been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product. Patients with [cardiovascular disorders](#) should be watched closely when [amitriptyline/chlordiazepoxide](#) is given [18].

2) The cardiovascular effects of [amitriptyline](#) (0.93 to 1.15 mg/kg/day) were compared with binedaline (1.85 to 2.31 mg/kg/day) in 8 healthy volunteers. Each volunteer received each medication plus placebo for 5 days, followed by 9-day washout periods. Both drugs caused significant [tachycardia](#). No other major changes in ECG or systolic time intervals were noted [27].

3.3.2] Dermatologic Effects

3.3.2.A] Photosensitivity

1) Photosensitivity has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

a) A 53-year-old man treated with [chlordiazepoxide](#) 25 to 75 mg/day orally for 2 weeks developed a photoallergic reaction characterized as eczematous following sun exposure. Following drug discontinuation and sun exposure avoidance, the reaction disappeared within 2 weeks. Rechallenge of the patient with the drug and exposure to light wave lengths between 220 and 3200 Angstroms resulted in a similar reaction occurring [73].

3.3.2.B] Rash

1) Skin rash has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Galactorrhea

1) [Galactorrhea](#) has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

a) A 24-year-old woman treated with [amitriptyline](#) 25 mg twice a day to 50 mg 3 times a day for more than 1.5 years developed [breast enlargement](#) and lactation. This developed in association with a tumor which extended from her pelvis to her umbilicus. Discontinuation of the drug and removal of her right ovary and a large pseudomucinous cyst resulted in resolution of the

breast enlargement and lactation within a few days. It was also noted that the patient received trifluoperazine in a dose of 1 mg twice a day, but the author postulated that this amount of drug was too small to cause the lactation experienced by this patient [51].

b)) A 41-year-old woman treated with chlordiazepoxide 10 mg 4 times a day orally with demeclocycline, nitrofurantoin, and methenamine mandelate developed lactation with secretions from both breasts followed by mammary enlargement and tenderness associated with tingling and pain in the nipples. Chlordiazepoxide was discontinued and the patient was treated with diethylstilbestrol 15 mg/day for one week without any appreciable effect. The patient was then treated with placebo capsules but these required discontinuation because of side effects. One month later, the breasts returned to normal and secretion completely disappeared. Reinstating chlordiazepoxide resulted in gynecomastia and copious milky secretions after 2 months. The author postulated that the probable mechanism was hypothalamic stimulation or suppression permitting anterior pituitary release of lactogenic hormone [52].

3.3.3.B] Gynecomastia

1)) Gynecomastia has been reported in patients receiving amitriptyline, chlordiazepoxide, or similar components, although it has not been reported with use of the combination amitriptyline/chlordiazepoxide product [18].

3.3.3.C] Hyperglycemia

1)) Elevation of blood glucose level has been reported in patients receiving amitriptyline, chlordiazepoxide, or similar components, although it has not been reported with use of the combination amitriptyline/chlordiazepoxide product [18].

a)) A 63-year-old diabetic woman taking 45 Units/day of NPH insulin took part in a study examining the influence of chlordiazepoxide on steroid metabolism. The patient was administered 40 mg/day of chlordiazepoxide and in 2 to 3 weeks, the patient's fasting blood glucose began to rise, plateauing at a level of 370 to 395 mg/dL. With continued chlordiazepoxide administration this blood glucose level was maintained and upon withdrawal of the drug, the glucose level dropped to a range of 260 to 280 mg/dL within 3 weeks [55].

3.3.3.D] Hypoglycemia

1)) Lowering of blood glucose level has been reported in patients receiving amitriptyline, chlordiazepoxide, or similar components, although it has not been reported with use of the combination amitriptyline/chlordiazepoxide product [18].

3.3.3.E] Increased body temperature

1)) A 41-year-old white man treated with oral amitriptyline 100 mg twice a day concomitantly with chlorpromazine and benztropine developed hyperpyrexia. While receiving all 3 drugs concomitantly the patient became comatose and responded only to deep pain. The patient's skin was noted to be hyperpigmented, red, hot, and dry. He was noted to have a rectal temperature of 107 degrees F associated with a sinus tachycardia of 135/min and tachypnea of 40/min. Treatment with intubation, oxygen, and cooling measures resulted in the reduction of the temperature to 100 degrees F in 40 minutes. The patient was maintained on a thermal blanket and his sensorium gradually cleared and body temperature returned to normal [56].

3.3.3.F] Syndrome of inappropriate antidiuretic hormone secretion

1j) Syndrome of [inappropriate antidiuretic hormone secretion](#) has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

a) A 66-year-old woman was treated with [amitriptyline](#) 50 mg in the morning and 100 mg at night for [manic depressive illness](#), depressed type. Ten weeks later the woman became lethargic, confused, and weak. Admission laboratory data revealed [hyponatremia](#), serum [hypotonicity](#), and relative urine hypertonicity. [Amitriptyline](#) was discontinued and the patient was put on fluid restriction. The patient showed a rapid improvement in serum chemistry. It was concluded that the patient was suffering from [hyponatremia](#) due to the syndrome of [inappropriate secretion of antidiuretic hormone](#) secondary to [amitriptyline](#) administration [53].

b) A 51-year-old woman treated with [amitriptyline](#) 50 mg 3 times a day was found in a comatose state 6 weeks after starting therapy. The patient experienced a generalized tonic [clonic seizure](#) after admission to the hospital. The patient recovered with discontinuation of the [amitriptyline](#) and fluid restriction. Laboratory values supported the diagnosis of SIADH [54].

c) A 51-year-old woman experienced sudden onset of confusion and lethargy after approximately 3 weeks of [amitriptyline](#) 100 mg/day. The patient met criteria for the syndrome of inappropriate antidiuretic hormone (SIADH) including decreased serum sodium and osmolality, continued excretion of sodium in the urine, urine less than maximally dilute, and no evidence of dehydration. The patient was treated successfully with fluid restriction. Two years later a similar reaction was noted when the patient inadvertently received [amitriptyline](#) [44].

3.3.3.G] Weight gain

1j) Increased body weight has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

a) The literature was evaluated with regard to weight gain secondary to psychotropic agents (neuroleptic agents, [lithium](#), MAO inhibitors, and [amitriptyline](#)). Available data indicates that weight increases are associated with all of these medications in a significant percentage of patients treated. It appears that [chlorpromazine](#), of the neuroleptic agents, has the greatest weight promoting potential, with [molindone](#) and [loxapine](#) the least. With regard to antidepressants, [amitriptyline](#) appears to promote weight gain significantly more than [imipramine](#) and [desipramine](#). [Caloric restriction](#) is the primary countermeasure to weight gain with all of these agents [57].

b) A series of 51 patients, age range 26 to 60 years, treated with 100 to 150 mg/day of [amitriptyline](#) for durations of 3 or 9 months developed weight gain as a side effect of drug therapy. The average weight gain after 3 months was noted to be 2 kg and after 9 months 2.5 kg. The differences were noted to be highly statistically significant and that these patients had an apparent dose-related craving for carbohydrates. Fasting [insulin](#) and glucose were not affected. Discontinuation of the drug resulted in weight loss with an average of 2.38 kg [58].

3.3.4] Gastrointestinal Effects

3.3.4.A] Bowel obstruction

1j) [Adynamic](#) or [paralytic ileus](#) has been associated with usual therapeutic doses of [amitriptyline](#). This adverse reaction may be preceded by lower abdominal or colicky upper abdominal pain in association

with vomiting. In some cases the syndrome may be preceded by loose stools followed by progressive constipation. Physical exam may demonstrate abdominal distention, markedly diminished or absent bowel sounds, empty rectum or a collapse of the large gut. Radiography will demonstrate distended coils of large intestine. Discontinuation of the drug is mandatory and in some cases [laparotomy](#) may be required [62][63].

3.3.4.B] Constipation

- 1) Incidence: frequently [18]
- 2) Constipation has been reported frequently in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].

3.3.4.C] Paralytic ileus

- 1) [Paralytic ileus](#) has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

3.3.4.D] Stomatitis

- 1) [Stomatitis](#) has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

3.3.4.E] Swollen abdomen

- 1) Incidence: frequently [18]
- 2) Bloating has been reported frequently in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].

3.3.4.F] Taste sense altered

- 1) Peculiar taste has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

3.3.4.G] Xerostomia

- 1) Incidence: frequently [18]
- 2) Dry mouth has been reported frequently in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].
 - a) In a study comparing side effects to oxaprotiline and [amitriptyline](#), a 43% reduction in salivary flow was noted after one week of treatment with 75 mg to 150 mg at bedtime in 102 outpatients with mild depression. The reduction in salivary flow continued to increase through the fifth week, when it reached 63% [59].
 - b) Decreased salivation and sedation were seen more commonly in a group of 10 normal subjects when administered oral [amitriptyline](#) 50 mg at 9:00 AM as opposed to 9:00 PM. The investigators determined that the absorption rate was faster in the morning than in the evening because of circadian effects on pharmacokinetics, leading to higher blood levels [60].
 - c) Following usual therapeutic doses of [amitriptyline](#), [xerostomia](#) or dry mouth may develop in association with complications of [oral moniliasis](#), gum shrinkage, inflammation of the oral

cavity, [stomatitis](#), cracking of the lips and mouth, [pseudomembrane formation](#), and [hairy tongue](#) with white or black or bald, beefy red tongue. The author noted these symptoms appeared to be more prevalent in patients who wore dentures and that many of the symptoms are as a result of associated monilial infection [61].

3.3.5] Hematologic Effects

3.3.5.A] [Anemia](#)

1) Two patients received [chlordiazepoxide](#) 20 to 30 mg/day for 1 to 2 years and developed [hypoplastic anemia](#) demonstrated by depressed [hemoglobin](#) levels and reduced red blood cell counts. In addition, [platelet](#) counts were depressed and [erythrocyte sedimentation](#) rate was elevated. Bone marrow demonstrated myeloid maturation arrest. Discontinuation of the drug and treatment with steroids and blood resulted in normal blood picture and bone marrow within one month [21].

3.3.5.B] [Granulocytopenic disorder](#)

1) Incidence: rare [18]

2) [Granulocytopenia](#) has been rarely reported in patients who received a combination of [amitriptyline/chlordiazepoxide](#). Periodic blood counts are recommended during prolonged therapy with [amitriptyline/chlordiazepoxide](#) [18].

3.3.5.C] [Myelosuppression](#)

1) [Bone marrow suppression](#) has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product. Periodic blood counts are recommended during prolonged therapy with [amitriptyline/chlordiazepoxide](#) [18].

3.3.5.D] [Thrombocytopenia](#)

1) [Thrombocytopenia](#) has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product. Periodic blood counts are recommended during prolonged therapy with [amitriptyline/chlordiazepoxide](#) [18].

2) A 37-year-old woman treated with [amitriptyline](#) 55 mg/day for 10 days for severe depression developed [thrombocytopenia](#). Although the patient was also receiving [spironolactone](#), [chlorothiazide](#), [reserpine](#), and thyroid, 2 days after initiating the [amitriptyline](#) therapy the patient developed mucous membrane and cutaneous bleeding. Treatment with 60 to 80 mg/day of [prednisone](#) was ineffective; after 10 days [amitriptyline](#) was discontinued and [platelet](#) levels immediately increased and rapidly returned to normal. The [prednisone](#) was subsequently tapered off and discontinued. The patient was noted by history to have had a similar reaction to [doxepin](#) which had responded to [prednisone](#). The temporal relationship between the onset of [thrombocytopenia](#) with the treatment of the 2 structurally similar drugs suggests a likely cause for the [thrombocytopenia](#) [19].

3.3.5.E] [Thrombocytopenic purpura](#)

1) [Purpura](#) has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product. Periodic blood counts are recommended during prolonged therapy with [amitriptyline/chlordiazepoxide](#) [18].

2)) A 32-year-old woman developed generalized [petechiae](#) after 1 week of treatment with [chlordiazepoxide](#) 5 mg/[clidinium bromide](#) 2.5 mg in a dose of 3 tablets/day for nervousness and fatigue associated with nonspecific gastrointestinal complaints. The patient's [platelet](#) count was found to be 12,000/mm(3) and was associated with a [bone marrow aspiration](#) that demonstrated an increased number of megakaryocytes. Discontinuation of [chlordiazepoxide](#)/[clidinium bromide](#) resulted in the patient's [platelet](#) count returning to normal within 5 days [20].

3.3.6] Hepatic Effects

3.3.6.A] Decreased liver function

1)) Incidence: rare [18]

2)) [Hepatic dysfunction](#) of uncertain etiology has been rarely reported in patients who received a combination of [amitriptyline](#)/[chlordiazepoxide](#). Liver function tests are recommended during prolonged therapy with [amitriptyline](#)/[chlordiazepoxide](#) [18].

a)) A 23-year-old man received a mixture of [amitriptyline](#) and [perphenazine](#) (Triavil(R)) and was changed after 4 months to a dose of [amitriptyline](#) 150 mg/day alone. Three months later, the patient developed elevated liver function tests with a resolution of serum transaminases to normal with discontinuation of the drug. Rechallenge with [amitriptyline](#) resulted in abrupt increases of the patient's SGOT and [alkaline phosphatase](#) levels. Liver function tests returned to normal over several weeks. The authors concluded that the [amitriptyline](#) was responsible for the drug-induced [hepatic dysfunction](#) [65]. Elevations in AST (aspartate transaminase) occurred in 4 of 36 patients receiving [chlordiazepoxide](#) 100 to 600 mg daily for longer than 3 months. AST remained elevated in only 1 patient [72].

3.3.6.B] Hepatotoxicity

1)) Usual therapeutic doses of [amitriptyline](#) have been reported to cause [hepatotoxicity](#). Clinically the disease may present with [jaundice](#), dark urine, pale stools, and elevated serum [bilirubin](#), SGOT, SGPT, and [alkaline phosphatase](#) levels. Discontinuation of the drug usually results in improvement of the liver disease although at least 1 case of death has been reported [64]. Based on available literature, [amitriptyline](#)-induced [hepatotoxicity](#) may result in distention of bile canaliculi with bile and retention of bile and liver cells or mild globular disarray and general ballooning of hepatocytes with mild parenchymal infiltration, mononuclear cells, and some eosinophils [65][66].

3.3.6.C] Intrahepatic cholestasis

1)) Three case reports describe [intrahepatic cholestasis](#) in patients receiving various doses of oral [chlordiazepoxide](#) for as short as 2 days and up to 3 years (occasional use). Two patients were icteric and liver biopsy in all 3 patients demonstrated [cholestasis](#) with mild to marked parenchymal changes. Discontinuation of the drug resulted in complete recovery within a few weeks in all patients [67].

3.3.6.D] Jaundice

1)) Incidence: rare [18]

2)) [Jaundice](#) has been rarely reported in patients who received a combination of [amitriptyline](#)/[chlordiazepoxide](#). Liver function tests are recommended during prolonged therapy with [amitriptyline](#)/[chlordiazepoxide](#) [18].

a)) [Jaundice](#) was reported in a 26-year-old woman who received [chlordiazepoxide](#) 210 mg orally for 2 weeks followed by 30 mg/day for 56 days. The patient presented with general malaise, nausea,

and anorexia which progressed to [pruritus](#) and [jaundice](#). [Chlordiazepoxide](#) was discontinued and the patient slowly improved [68].

b) [Jaundice](#) and [hepatic necrosis](#) occurred in a 64-year-old woman receiving oral [chlordiazepoxide](#) 10 mg 3 times daily for 12 days. In 3 weeks, the patient developed painless [jaundice](#) with dark urine and pale stools. Liver function tests, including serum [bilirubin](#), [ALT](#) (alanine transaminase), and [alkaline phosphatase](#), were elevated. Liver biopsy demonstrated massive reticulum collapse of bile ductules and portal tracts with excessive fibrous tissue. Subsequently, edema and ascites developed. The patient was treated with [prednisolone](#) and steadily improved [69].

c) A 51-year-old man treated with [chlordiazepoxide](#) 25 mg/day orally for 4 to 5 weeks developed epigastric burning, nausea, vomiting, and [pruritus](#) followed by [jaundice](#). Liver biopsy demonstrated portal areas infiltrated by neutrophils, [lymphocytes](#), and eosinophils. Some bile canaliculi were dilated with evidence of [bile stasis](#) and scattered degeneration of parenchymal cells. [Chlordiazepoxide](#) was thought to be the hepatotoxic agent, based on laboratory and histologic data [70].

d) [Fulminant hepatitis](#) occurred on two occasions in a 51-year-old woman during [amitriptyline](#) therapy. Fever and [jaundice](#) were present on both occasions. The first episode occurred following 430 days of treatment with [amitriptyline](#) 30 mg daily; withdrawal of the drug resulted in resolution of symptoms. The second episode occurred when the patient resumed [amitriptyline](#) 30 mg daily one month later. Following 12 days of treatment, the patient became jaundiced and developed [hepatic encephalopathy](#), [ascites](#), increased prothrombin time, and massive [hepatic necrosis](#). Withdrawal of the drug once again resulted in complete recovery, although [jaundice](#) persisted for approximately 2 months. The mechanism of action of amitriptyline-induced [hepatitis](#) remains obscure, as there is evidence for both direct toxicity and an immunologic mechanism [71].

3.3.8] Musculoskeletal Effects

3.3.8.A] Myalgia

1) A 56-year-old woman treated with [amitriptyline](#) 300 to 400 mg at bedtime developed muscle cramps or a pulling feeling in her calves. Discontinuation of the drug resulted in resolution of the cramps, but when the drug was resumed the cramps recurred [74].

3.3.9] Neurologic Effects

3.3.9.A] Ataxia

1) Ataxia has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

3.3.9.B] Confusion

1) Confusion has been reported in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].

2) A high number of geriatric patients on tricyclic antidepressant therapy have developed confusional reactions characterized as restlessness, sleep disturbances, forgetfulness, agitation, disorientation, and delusions. This reaction does not appear to be dose related and is possibly due to the central anticholinergic effects of these drugs. These episodes have been reported to develop within the first 2 weeks of drug therapy and are usually self-limiting, lasting from 3 to 20 days. However, reduction of dosage or discontinuation of the drug appears to result in resolution of these confusional reactions more quickly [40].

3.3.9.C] Dizziness

- 1) Incidence: frequently [18]
- 2) Dizziness has been reported frequently in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].

3.3.9.D] Dyskinesia

- 1) Two patients, age 37 and 44 years, treated with [amitriptyline](#) 50 mg 3 times a day to 200 mg 4 times a day, developed facial [dyskinesias](#) characterized as bucco-facio-lingual [dyskinesias](#) in association with gross athetotic movements. Discontinuation of [amitriptyline](#) resulted in resolution of the symptoms [39].

3.3.9.E] Electroencephalogram abnormal

- 1) Changes in EEG patterns have been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

3.3.9.F] Extrapyramidal movements

- 1) Extrapyramidal symptoms have been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

3.3.9.G] Impaired psychomotor performance

- 1) [Amitriptyline](#) has been reported to cause decreased psychomotor performance. [Amitriptyline](#) 50 mg was compared with placebo and zimelidine 200 mg in an acute, single-dose, crossover study in 9 female volunteers. [Amitriptyline](#) caused significant sedation, increased brake reaction time and increased choice reaction time when compared with both placebo and zimelidine [31].
- 2) Incoordination following usual therapeutic doses of [amitriptyline](#) has been reported. Discontinuing the drug usually results in complete recovery of the patient [32][33].
- 3) [Biofeedback](#) training has been used to control vascular and neuromuscular pain syndromes. The effect of [amitriptyline](#) and [propranolol](#) on learning [biofeedback](#) was studied in 60 patients. Much more variability in learning occurred in those patients receiving either [propranolol](#) or [amitriptyline](#) compared to those patients receiving either both or no medication, although all patients eventually reached training criteria. The increased training time could result in patient frustration and noncompliance with training [34].

3.3.9.H] Paresthesia

- 1) Paresthesias of the extremities have been reported in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].
- 2) Paresthesias have been reported following use of usual therapeutic doses as low as [amitriptyline](#) 20 to 25 mg 3 times a day. Paresthesias may involve various parts of the body and may tend to affect only 1 side of the body and face. In addition, weakness of the limbs may occur, with speech impediments developing. Discontinuation of [amitriptyline](#) usually results in resolution of the symptoms [41][42].

3.3.9.I] Seizure

- 1) [Epileptic convulsions](#) of a grand mal type have been reported following the use of [amitriptyline](#) in usual therapeutic doses in patients without any previous seizure disorders [35][36]. However, precipitation of

convulsions may occur in patients with a history of [epilepsy](#) previously well controlled. Thus, in patients with low seizure thresholds, concomitant use of the anticonvulsant drug appears to be mandatory [37].

2) [Spike-wave stupor](#) occurred in a 58-year-old man who was being treated with [amitriptyline](#) 150 mg/day for a depressive cycle of manic/[depressive disorder](#). [Spike-wave stupor](#), resembling [petit mal status](#) but dissimilar in some respects, had occurred but was unrecognized upon a previous exposure to [amitriptyline](#). Discontinuation of the drug and treatment with [diazepam](#) cleared the epileptiform episode. Similar reports from the clinical literature involving other tricyclic antidepressants are reviewed by the authors [38].

3.3.9.J] Somnolence

1) Incidence: frequently [18]

2) Drowsiness has been reported frequently in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].

3) The Boston Collaborative Drug Surveillance Program reports that a higher percentage of nonsmoking or light-smoking patients receiving [chlordiazepoxide](#) developed drowsiness than patients who are heavy smokers. Drowsiness appears to be a dose related phenomenon and heavy smokers tend to have a lower incidence of this side effect, probably due to increased metabolism [49].

4) In a series of over 1000 patients with a mean age of 51 years, drowsiness represents a frequent adverse effect (reported in 103 patients). A trend for this to correlate with low serum albumin was noted but was not statistically significant. This association was not influenced by factors such as age, sex, renal function, or length of hospital stay [50].

3.3.9.K] Tremor

1) Tremor has been reported in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].

2) Other reports have associated [amitriptyline](#) in usual therapeutic doses to side effects such as agitation, tremulousness, hallucinations, anxiety, and psychotic manifestations [43][44][45][46][47][48].

3.3.10] Ophthalmic Effects

3.3.10.A] Blurred vision

1) Incidence: frequently [18]

2) Blurred vision has been reported frequently in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].

3.3.12] Psychiatric Effects

3.3.12.A] Aggressive behavior

1) Four cases of rapid-onset, untoward aggressiveness associated with the use of tricyclic antidepressants were reported. In the first 2 cases, the aggressive behavior coincided with the reintroduction of the tricyclic antidepressant. The mechanism of the paradoxical response of rapid onset and qualitative characteristics of the reaction are consistent with a probable site of action in the reticular formation, which is the rationale for their usefulness in [cataplexy](#) [75].

2) A number of studies have indicated that [chlordiazepoxide](#) may increase hostility [76][77].

3.3.12.B] Delirium

1) In patients treated with [amitriptyline](#), a blood level of [amitriptyline/nortriptyline](#) in excess of 450 nanograms (ng)/mL appears to be a good predictor of [delirium](#) as an adverse effect. Blood level assays were performed on 100 patients taking doses ranging from 100 to 250 mg/day. Of these, 14 had levels exceeding

300 ng/mL, significantly above the therapeutic range of 150 to 250 ng/mL. Of these, 6 patients exhibited drug-induced [delirium](#). All 6 patients who exhibited [delirium](#) had levels exceeding 450 ng/mL [79].

3.3.12.C] Depression, Worsening

1) While evidence exists from placebo-controlled maintenance trials in adults with depression to substantiate a delay in the recurrence of depression with antidepressant use, clinical worsening of depression has been reported in patients receiving antidepressant therapy, particularly during the initial few months of treatment. It may persist until significant remission occurs. All patients treated with antidepressants for any indication should be monitored for signs of clinical worsening [18].

2) Adult and pediatric patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), or mania may be at risk of worsening of their depression. This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms [18].

3.3.12.D] Dream disorder

1) Vivid dreams have been reported in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].

3.3.12.E] Hallucinations

1) Hallucinations have been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

a) Seven patients (age range 18 to 52 years) receiving [chlordiazepoxide](#) 10 to 100 mg at bedtime by various routes developed visual hallucinations after drug administration, particularly at bedtime. However, it was noted that reality testing in these patients was unimpaired since they recognized the hallucinations as being unreal. The hallucinations were characterized as being about 5 minutes or shorter in length and occurred during some phase of sleep. They usually were terminated on waking or being awakened by a voice of a second party. Discontinuation of the drug resulted in disappearance of the hallucinations; however, reinstitution of [chlordiazepoxide](#) resulted in reappearance of the hallucinations [78].

b) Other reports have associated [amitriptyline](#) in usual therapeutic doses to side effects such as agitation, tremulousness, hallucinations, anxiety, and psychotic manifestations [43][45][46][47][48].

3.3.12.F] Hypomania

1) [Hypomania](#) has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

3.3.12.G] Mania

1) Three cases of mania were reported in patients with [bipolar disorder](#) experiencing an episode of [major depression](#) and receiving [amitriptyline](#) (125 to 175 mg/day) and [isocarboxazid](#) (30 to 50 mg/day). These patients had all proven unresponsive to either drug alone, and began to develop mania at 5 to 9 weeks after initiation of combined therapy. Improvement was seen within 1 to 2 weeks after dosages were reduced [80].

3.3.12.H] Suicidal thoughts

1J) In a pooled analyses of placebo-controlled trials in adults with [major depressive disorder](#) or other psychiatric disorders including 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in greater than 77,000 patients, the risk of suicidality varied among the drugs studied. However, for almost all drugs studied, there was a tendency toward increasing suicidality in younger patients. The risk difference (drug versus placebo in the number of cases of suicidality per 1000 patients treated) was 14 additional cases in patients less than 18 years of age, 5 additional cases in patients 18 to 24 years, 1 fewer case in patients 25 to 64 years, and 6 fewer cases in patients 65 years and older. No suicides occurred in the pediatric trials. Suicides did occur in the adult trials; however, the number of suicides was insufficient to determine causality. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known [18].

2J) Adult and pediatric patients being treated with antidepressants for [major depressive disorder](#) who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), or mania may be at risk of [suicidal ideation](#) and behavior (suicidality). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms [18].

3J) A causal role for antidepressants in inducing suicidality has been established in pediatric patients [81]. While [amitriptyline/chlordiazepoxide](#) is not approved for use in pediatric patients [18], 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 9 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 [81].

3.3.12.I] Suicide

1J) In a pooled analyses of placebo-controlled trials in adults with [major depressive disorder](#) or other psychiatric disorders including 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in greater than 77,000 patients, the risk of suicidality varied among the drugs studied. However, for almost all drugs studied, there was a tendency toward increasing suicidality in younger patients. The risk difference (drug versus placebo in the number of cases of suicidality per 1000 patients treated) was 14 additional cases in patients less than 18 years of age, 5 additional cases in patients 18 to 24 years, 1 fewer case in patients 25 to 64 years, and 6 fewer cases in patients 65 years and older. No suicides occurred in the pediatric trials. Suicides did occur in the adult trials; however, the number of suicides was insufficient to determine causality. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known [18].

3.3.13] Renal Effects**3.3.13.A] Urinary retention**

1J) Urinary retention has been reported in patients receiving [amitriptyline](#), [chlordiazepoxide](#), or similar components, although it has not been reported with use of the combination [amitriptyline/chlordiazepoxide](#) product [18].

3.3.14] Reproductive Effects

3.3.14.A] Erectile dysfunction

1J) Impotence has been reported in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].

3.3.14.B] Sexual dysfunction

1J) The effects of mianserin 60 mg/day were compared with [amitriptyline](#) 150 mg/day on nocturnal sexual arousal in 6 normal subjects in a double-blind, placebo-controlled, crossover study. Measurement of frequency, amplitude, and duration of penile tumescence during sleep was done after 2 weeks of drug therapy. Mianserin and [amitriptyline](#) decreased tumescence and duration of erection equally and significantly more than placebo [82].

2J) Seven cases of impotence have been described with [amitriptyline](#) therapy, with a minimum daily dose of 50 mg [83][84][85][86][87]. Loss of libido and impotence was suggested in another 3 cases, but details were not provided [88].

3J) Ejaculatory dysfunction has been described in 3 patients receiving a minimum dose of [amitriptyline](#) 100 mg/day [89][85]. Decreased libido has also been reported [90][85].

4J) A 41-year-old man treated with [chlordiazepoxide](#) 10 mg 3 times a day for 2 months for chronic anxiety developed delay and failure of ejaculation. Discontinuation of the drug resulted in normal sexual function. The author postulated that depression of spinal reflexes may be in part responsible for sexual dysfunction related to the drug [91].

3.3.15] Respiratory Effects

3.3.15.A] Nasal congestion

1J) Nasal congestion has been reported in patients who received a combination of [amitriptyline/chlordiazepoxide](#) [18].

3.3.16] Other

3.3.16.A] Drug dependence

1J) A 37-year-old woman was initially treated with [chlordiazepoxide](#) 10 mg 3 times a day and 20 mg in the evening and had self-administered 20 mg 5 times/day and 40 mg in the evening over several years. Following discontinuation of the drug, the patient developed withdrawal symptoms characterized by abdominal cramps, sweating, and crawling sensation under the skin. After reinstituting [chlordiazepoxide](#) the symptoms subsided but when the drug was withdrawn again, the symptoms recurred [92]. According to another report, after doses of 15 mg 3 times a day, an [abstinence syndrome](#) can occur following abrupt withdrawal of [chlordiazepoxide](#) after 16 weeks of therapy [93].

3.3.16.B] Hiccoughs

1J) A 19-year-old man treated with oral [chlordiazepoxide](#) 10 mg 4 times a day for 3 days developed hiccups within 1 hour of the first capsule. Hiccups persisted despite holding of breath and bag breathing but did not occur when the patient was asleep. After 3 days, the drug was discontinued and the hiccups ceased after

5 hours. Rechallenge of the patient with [chlordiazepoxide](#) the next day resulted in the hiccups recurring within 1 hour and persisting for 2 to 3 hours [99].

3.3.16.C] Increased drug tolerance

1j) Two cases of apparent development of tolerance to [amitriptyline](#) were reported. In the first case, a female patient with depression remained responsive to 150 mg/day for 6 months, but then relapsed. She again responded to 200 mg/day, but over the succeeding 3 years, relapsed when the dose fell below 150 mg/day on 3 occasions. A fourth recurrence failed to respond to 250 mg/day. In the second case, a female patient with depression responded to 100 mg/day for one year. After recurrence, control was again achieved with 200 mg/day. After one month, symptoms returned and the dose was increased to 250 mg/day, which was effective only for several weeks [94].

3.3.16.D] Withdrawal sign or symptom

1j) Withdrawal symptoms, including convulsions, tremor, abdominal and muscle cramps, vomiting, sweating, [dysphoria](#) and insomnia have been reported with abrupt discontinuation of benzodiazepines, including [chlordiazepoxide](#). The more severe symptoms are usually related to higher dosages and longer usage, but withdrawal symptoms can occur in patients given therapeutic dosages for shorter periods of time. Withdrawal symptoms such as nausea, headache, and malaise have also been reported with abrupt discontinuation of [amitriptyline](#). A gradual tapering schedule of [amitriptyline](#)/[chlordiazepoxide](#) should be used in patients who have taken an extended course of treatment [18].

a) The long-term daily use of benzodiazepines (at least 3 months) in therapeutic doses is associated with a mild but significant withdrawal syndrome after discontinuation. Withdrawal symptoms were different than those of anxiety, and included involuntary movements, paresthesias, perceptual changes, and confusion. Withdrawal symptoms reportedly occurred sooner in patients who had been receiving the shorter-acting benzodiazepines as compared with those receiving longer-acting agents; symptoms resolved after a period of 4 weeks [95].

b) In a study examining biochemical effects of abrupt discontinuation of tricyclic antidepressant therapy, anxious [dysphoria](#), [hypomania](#) characterized by mood elevation, grandiose ideation, pressured speech, increased motor activity, and panic attacks occurred in a patient after discontinuation of [amitriptyline](#) 250 mg/day. During therapy, the patient had exhibited depression, anergy, and hopelessness. The authors cited several other cases of withdrawal reactions from the clinical literature [96].

c) A mild withdrawal syndrome occurred in 8 of 10 subjects whose [amitriptyline](#) therapy (50 to 250 mg/day) was decrementally tapered in 3 steps over 3 weeks. The syndrome consisted of irritability, dream and sleep disturbance, and restlessness, and in all instances occurred within 2 weeks of the start of tapering [97].

d) The effects of abrupt discontinuation of [amitriptyline](#) (150 to 250 mg/day) were studied in 4 patients treated for depression. One patient exhibited a clear increase in anxiety, but other observed symptoms were not significantly altered [96].

e) An 8-year-old child treated with [amitriptyline](#) (30 to 50 mg at bedtime) for 7 months for behavioral problems experienced withdrawal symptoms upon discontinuation of [amitriptyline](#). A recent course of [methylphenidate](#) was not effective. Recurrence of behavioral symptoms prompted discontinuation of the [amitriptyline](#). Two days later the child began to have severe nausea, vomiting, and abdominal cramps. Infection was ruled out by absence of fever, normal WBC, and no similar illness among close contacts. After 2 weeks, all symptoms resolved. The authors

attributed the child's severe reaction to the abrupt withdrawal of the anticholinergic influence of amitriptyline [98].

3.4| Teratogenicity/Effects in Pregnancy/Breastfeeding

A| Teratogenicity/Effects in Pregnancy

1| Amitriptyline

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

1| 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.

b| Australian Drug Evaluation Committee's (ADEC) Category: C

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

c| Crosses Placenta: Yes

d| Clinical Management

1| Due to reported teratogenic effects, use of amitriptyline during pregnancy should be avoided if possible, especially during the first trimester. The dangers of failure to treat major depression, however, are obvious, and in each case these dangers must be weighed against the potential for teratogenic effects. If pregnancy occurs during treatment, the patient should be advised of possible consequences to the fetus.

e| Literature Reports

1| Amitriptyline has been associated with teratogenic effects in both human case reports and animal studies; however, a clear causal relationship has not been established. In a large cohort study, of 21 mother-child pairs exposed to amitriptyline during the first trimester, no malformations were reported [1055].

2| A female received amitriptyline 10 mg three times daily for 24 days during the first trimester of pregnancy. Amitriptyline was discontinued as soon as pregnancy was diagnosed which was approximately 2 months after her last menstrual period. She subsequently gave birth to a male infant born with malformed left leg which was half the length of the right leg with a rudimentary foot. x-ray examination revealed an absent fibula, a hypoplastic tibia and a hypoplastic foot. It was also noted that the patient received prochlorperazine as well [1056]. A definite cause-effect relationship was not established in this particular report.

3| A mother ingested a combination of amitriptyline and perphenazine in a suicide gesture at 8 days gestation. The infant was born with multiple congenital defects such as

microcephaly, "cotton- like" hair with pronounced shedding, cleft palate, micrognathia, ambiguous genitalia, and dermal ridges[1057].

4j) Based on data collected through the Motherisk Program, there appear to be no differences in cognitive function, temperament, and general behavior in children exposed to amitriptyline throughout gestation as compared to controls. However, among infants who were exposed to either fluoxetine or tricyclic antidepressants throughout gestation, those born to mothers with uncontrolled depressive symptoms showed lower cognitive and language achievements than those born to mothers who were well-controlled [1058].

2j) Chlordiazepoxide

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

1j) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

b) Crosses Placenta: Yes

c) Clinical Management

1j) All benzodiazepines can be expected to cross the placenta. Teratogenicity with chlordiazepoxide has not been confirmed; however, other benzodiazepines have demonstrated teratogenic potential [1049]. Use of chlordiazepoxide during pregnancy, especially during organogenesis (6 and 10 weeks of pregnancy) is not recommended. If pregnancy occurs during chronic use, the patient should be advised of the desirability of discontinuing the drug and of possible consequences to the fetus. If use is unavoidable, prescribe as monotherapy in the lowest effective dosage, for the shortest duration possible, and in divided doses to avoid high peak concentrations. Additionally, both the mother and fetus should be monitored [1050][1051]. In contrast to benzodiazepines, the non-benzodiazepines zolpidem and zaleplon are in Pregnancy Risk Categories B and C, respectively [1052][1053].

d) Literature Reports

1j) Although animal studies with chlordiazepoxide have shown evidence of teratogenicity, human data has produced conflicting evidence. In an epidemiologic study, chlordiazepoxide use during the first 42 days of pregnancy revealed a greater than 4-fold increase in severe congenital abnormalities, and an increase in fetal mortality [1042]. Similarly, chlordiazepoxide exposure was possibly linked to congenital heart disease in a survey of 390 infants with congenital heart disease [1043]. A single case has been reported of aplasia cutis congenita in a neonate born to a mother who had used lorazepam and diazepam or chlordiazepoxide in the early part of her pregnancy; however, a direct causal relationship could not be clearly established nor other causes ruled out [1044]. Furthermore, first trimester use of chlordiazepoxide could not be associated with an increased defect rate in

a report on almost 50,000 pregnancies [1045] or a case-control study of nearly 1500 infants [1046].

2j) In a retrospective case control study of 43 pregnant Hungarian women who attempted suicide with nitrazepam or other benzodiazepines (mean nitrazepam dose 204 mg) between 1960 and 1993, 13 of their exposed children were born with congenital abnormalities (30.2%) compared with 3 of their unexposed siblings (10.3%, n=29) (odds ratio 3.8, 95% confidence interval, 1 to 14.6). Congenital abnormalities (CAs) were present in 7 children exposed to nitrazepam alone or with other drugs between postconception weeks 3 and 12, including 3 cases of congenital inguinal hernia, 1 case of torticollis, 1 case of pectus excavatum, complex CA of the respiratory system, and 1 case of multiple CAs with talipes equinovarus, mild microcephaly, and 5 other mild anomalies and borderline fetal alcohol syndrome (FAS). CAs that occurred in the 6 children exposed after postconception week 12 included 2 cases of congenital inguinal hernia, 1 case of bronchial stenosis, and 3 cases of multiple CAs, including FAS with talipes equinovarus and low IQ; borderline FAS with mild microcephaly and talipes equinovarus with 11 minor abnormalities; and talipes equinovarus with 4 minor abnormalities. Their unexposed siblings with CAs were affected with cleft lip and palate, ventricular septal defect, and FAS. Most CAs were classified as mild deformations. Researchers note concomitant exposure to other drugs, tobacco smoke, and alcohol in several of the exposed children as potential confounds [1047].

3j) Mixed results were found in a meta-analysis of cohort and case-control studies that reported on the occurrence of major malformations in infants exposed to any benzodiazepine during at least the first trimester of pregnancy [1048]. When only cohort studies were pooled, no significant association between benzodiazepine use and major malformations was noted (odds ratio 0.90; 95% confidence interval 0.61 to 1.35; p=0.62); data pooled from case-control studies, however, showed a positive association with major malformations (odds ratio 3.01; 95% confidence interval 1.32 to 6.84; p=0.008). Similar observations were made with regard to oral cleft; the pooled cohort study data did not substantiate an association with drug use (odds ratio 1.19; 95% confidence interval 0.34 to 4.15; p=0.997), whereas the case-controlled data did (odds ratio 1.79; 95% confidence interval 1.13 to 2.82; p=0.01). Finally, the meta-analysis found two case-control studies that each provided conflicting evidence of any association between benzodiazepine exposure and cardiac malformations, and one study failed to find an association between exposure and central nervous system defects.

4j) Neonatal withdrawal symptoms, including severe tremor and irritability, have been associated with the use of chlordiazepoxide during pregnancy [1046]. In follow up on infants born to mothers who had taken chlordiazepoxide during pregnancy, no difference was found in infant intelligence quotient (IQ) scores at four years of age nor in mental and motor status scores at eight months of age [1045].

Bj) Breastfeeding

1j) Amitriptyline

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

bj) World Health Organization Rating: Compatible with breastfeeding.

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

1) 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.

d) Clinical Management

1) Existing data indicate that very little amitriptyline and nortriptyline (active metabolite) would be ingested by a breastfeeding infant and that maternal use of amitriptyline during breastfeeding is probably safe. However, the prolonged half-life of nortriptyline in newborns suggests that some infants may be at risk of accumulation. If the patient elects to breastfeed during amitriptyline therapy, the infant should be monitored for adverse effects.

e) Literature Reports

1) In one report, ingestion of amitriptyline 100 mg daily produced serum levels of 83 to 141 ng/mL. Levels of 135 to 151 ng/mL were found in the breast milk however, no trace of amitriptyline was detected in the infant's serum [1061]. Two case reports evaluated the distribution of amitriptyline in breast milk. Milk amitriptyline concentration means were 88 and 143 ng/mL, respectively, and milk nortriptyline concentration means were 69 and 55 ng/mL. Milk plasma ratios ranged from 1.35 to 1.7 for amitriptyline, and from 0.79 to 1.1 for nortriptyline. Plasma amitriptyline and nortriptyline concentrations were less than 10 ng/mL in the breastfeeding infants [1062].

2) The safe use of amitriptyline during breastfeeding has been reported. A 30-year-old woman received a sustained-release preparation of amitriptyline beginning 3.5 months after delivery and the woman continued to breastfeed. No active drug was observed in the infant serum and no clinical signs of intoxication were reported [1063].

2) Chlordiazepoxide

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

1) 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.

b) Clinical Management

1) There is insufficient information available regarding the use of chlordiazepoxide during breastfeeding to establish its safety. It is unknown if chlordiazepoxide given chronically during breastfeeding will result in a pharmacologically significant exposure for the breastfeeding infant. Side effects such as lethargy, sedation, and weight loss could possibly occur in infants if nursed by mother on chlordiazepoxide. It is recommended that physicians monitor nursing infants for these effects and discontinue breastfeeding if they

are noted. Because the risks of prolonged use during breastfeeding have not been fully elucidated, caution is advised [1050].

c) Literature Reports

1) There have been no case reports or published clinical data regarding the use of chlordiazepoxide during breastfeeding.

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] Abiraterone

- 1) Interaction Effect: increased exposure of [amitriptyline](#)
- 2) Summary: Concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#). Poor metabolizers are especially at risk. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and adjust the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#), especially in poor metabolizers. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and reduce the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amitriptyline](#)

3.5.1.B] Acecainide

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[330], [amiodarone](#) [331], [azimilide](#) [332], [bretylum](#) [333], [ibutilide](#) [334], [sematilide](#) [335], [dofetilide](#) [336], and [sotalol](#) [337]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [338][339].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [328].

b)) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised [329].

3.5.1.C] Aceclofenac

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: unknown

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.D] Acemetacin

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: unknown

8)) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.E] Acenocoumarol

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[931][932]. Considerable interindividual differences may be found [933].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: In patients receiving tricyclic antidepressants and oral [anticoagulant therapy](#), the prothrombin time ratio or INR ([international normalized ratio](#)) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of [anticoagulation](#) may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
- 7) Probable Mechanism: decreased acenocoumarol metabolism; increased acenocoumarol absorption
- 8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of [nortriptyline](#) or [amitriptyline](#) resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects [928]. This effect was not observed with [warfarin](#).

b) A single oral dose of bishydroxycoumarin after 8 days of [nortriptyline](#) resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers [929]. The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term [anticoagulant therapy](#) who used concurrent TCAs [930]. TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.F] Albuterol

- 1) Interaction Effect: an increased risk of cardiovascular system effects (eg, [tachycardia](#), blood pressure changes)
- 2) Summary: [Albuterol](#) should be administered with extreme caution to patients being treated with tricyclic antidepressants (TCAs), or within 2 weeks of TCA discontinuation, because the action of [albuterol](#) on the vascular system may be potentiated. Consider alternative therapy in patients using TCAs[746]. If concomitant administration is required, monitor the patient closely.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Albuterol](#) should be administered with extreme caution to patients being treated with tricyclic antidepressants (TCAs), or within 2 weeks of TCA discontinuation. Concomitant use of [albuterol](#) and TCAs may potentiate the action of [albuterol](#) on the vascular system. Consider alternative therapy in patients using TCAs[746]. If concomitant administration is required, monitor the patient closely.
- 7) Probable Mechanism: potentiation of vascular effects of [albuterol](#)

3.5.1.G] Alfentanil

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.H] Alfuzosin

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Both [alfuzosin](#) and [amitriptyline](#) have been associated with QT prolongation[426][236]. Use caution when using [alfuzosin](#) and [amitriptyline](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [426]. If concomitant therapy is required, monitor the patient closely for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [alfuzosin](#) and [amitriptyline](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[426]. If concomitant therapy is required, monitor the patient closely for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.I] Almotriptan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[236], and [almotriptan](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment and at dosage increases is recommended if [almotriptan](#) and [amitriptyline](#) are used concurrently [779]. 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 [240].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [almotriptan](#) and [amitriptyline](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, monitoring of patient during treatment and dosage increases is recommended[779].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.J] Amifampridine

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

2J) Summary: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#)[963].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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](#)[963].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.K] Amiodarone

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

2J) 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](#)[372].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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](#)[372].

7J) Probable Mechanism: additive effects on QT interval

3.5.1.L] Amisulpride

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

2J) Summary: Use caution with the concomitant use of amisulpride with other agents that prolong the QT interval and monitor the patient's heart rhythm prior to coadministration. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such as [torsade de pointes](#)[643].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6) Clinical Management: Use caution with the concomitant use of amisulpride with other agents that prolong the QT interval and monitor the patient's heart rhythm prior to coadministration. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such [torsade de pointes](#)[643].

7) Probable Mechanism: additive QT prolongation

3.5.1.M] [Amobarbital](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[142][143][144][145][146].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [133][134][135][136][137].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [138]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [139]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [140]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [141].

3.5.1.N] [Amobarbital](#)

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a)) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.O] [Amoxapine](#)

- 1)) Interaction Effect: an increased risk of QT interval prolongation
- 2)) Summary: Concomitant use of [amitriptyline](#) and [amoxapine](#) is not common clinical practice. However if using [amitriptyline](#) and [amoxapine](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [amitriptyline](#) and [amoxapine](#) is not common clinical practice. However if using [amitriptyline](#) and [amoxapine](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].
- 7)) Probable Mechanism: additive effects on the QT interval

3.5.1.P] [Amphetamine](#)

- 1)) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2)) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[721].
- 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[721].
- 7)) Probable Mechanism: additive serotonergic effect

3.5.1.Q] [Amprenavir](#)

- 1)) Interaction Effect: increased tricyclic agent serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2)) Summary: Coadministration of [fosamprenavir](#) with a tricyclic antidepressant may provoke increased serum concentrations of the tricyclic antidepressant, causing a potential risk of [arrhythmias](#) or other serious adverse effects. [Fosamprenavir](#) is a prodrug of [amprenavir](#), an inhibitor of the CYP3A4 isoenzyme

in addition to being a CYP3A4 substrate. Tricyclic agents may partially depend on the CYP3A4 pathway for metabolism. Plasma concentrations of the tricyclic agent should be closely monitored in patients also receiving [fosamprenavir](#)[412].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: If concomitant therapy with [fosamprenavir](#) and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic agent should be closely monitored. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))[412].

7) Probable Mechanism: inhibition of CYP3A4-mediated tricyclic agent metabolism

3.5.1.R| Amtolmetin Guacil

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.S| Anagrelide

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

2) 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](#)[894].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) 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](#)[894].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.T] Anileridine

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.U] Anisindione

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[957][958]. Considerable interindividual differences may be found [959].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: In patients receiving tricyclic antidepressants and oral [anticoagulant therapy](#), the prothrombin time ratio or INR ([international normalized ratio](#)) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of [anticoagulation](#) may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
- 7) Probable Mechanism: decreased [anisindione](#) metabolism; increased [anisindione](#) absorption
- 8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of [nortriptyline](#) or [amitriptyline](#) resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects [954]. This effect was not observed with [warfarin](#).

b) A single oral dose of bishydroxycoumarin after 8 days of [nortriptyline](#) resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers [955]. The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term [anticoagulant therapy](#) who used concurrent TCAs [956]. TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.V] [Apomorphine](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [apomorphine](#) and [amitriptyline](#) may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#). Therefore, caution should be used when these agents are given concurrently[236][237]. If concurrent use is required, monitor closely for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [apomorphine](#) and [amitriptyline](#) may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#). Therefore, caution should be used when these agents are given concurrently[236][237]. If concurrent use is required, monitor closely for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.W] [Aprindine](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended[467][468][469].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [465].

b) A 68-year-old man suffering from agitated [major depression](#) was begun on a dose of [desipramine](#) 125 mg daily which produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An increased dose of 175 mg daily produced excellent clinical response with no side effects. He developed [atrial fibrillation and flutter](#). [Digoxin](#) 0.25 mg daily was added to his therapy, and [desipramine](#) was discontinued. His [arrhythmia](#) was suppressed with the addition of [propafenone](#) 150 mg twice daily and 300 mg at bedtime. [Desipramine](#) 150 mg daily was again begun, at which point he experienced dry mouth, sedation, and shakiness; the [desipramine](#) serum level was measured at 2092 nmol/L. The [desipramine](#) was discontinued for five days, the

side effects ceased, and [desipramine](#) therapy was resumed at 75 mg daily. The [desipramine](#) serum level was measured at 1130 nmol/L [466].

3.5.1.X] Aprobarrital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.Y] Arbutamine

1) Interaction Effect: unreliable [arbutamine](#) test results

2) Summary: Because tricyclic antidepressants may affect heart rate, [arbutamine](#) should not be administered to a patient receiving a tricyclic antidepressant, since [arbutamine](#) test results may be unreliable[926].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Arbutamine](#) should not be administered to a patient receiving tricyclic antidepressant therapy.

7) Probable Mechanism: alteration of heart rate by the tricyclic antidepressant

3.5.1.Z] Arformoterol

1) Interaction Effect: an increased risk of cardiovascular excitation

2) Summary: Concurrent administration of [arformoterol](#) with a tricyclic antidepressant (TCA) may lead to potentiation of [arformoterol's](#) adrenergic effects on the cardiovascular system. Therefore, extreme

caution is advised if [arformoterol](#) is administered to patients who are being treated with a TCA[922]. Monitor patients closely for adverse cardiovascular effects.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Extreme caution and close observation for adverse cardiovascular effects are warranted when [arformoterol](#) is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects of [arformoterol](#) can be potentiated by TCAs[922].

7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.AA] [Aripiprazole](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[1005], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[1005], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AB] [Arsenic Trioxide](#)

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

2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with [arsenic trioxide](#). Possible pharmacodynamic interactions can occur between [arsenic trioxide](#) and potentially arrhythmogenic agents such as tricyclic antidepressants that prolong the QT interval[500]. Even though no formal drug interaction studies have been done, the coadministration of [arsenic trioxide](#) and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [501][502].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of [arsenic trioxide](#) and other drugs that may prolong the QTc interval, such as tricyclic antidepressants is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving [amitriptyline](#), compared to zero out of 53 in the control group using a hospital based information system. The authors recommended that [amitriptyline](#) not be used in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful [497][498].

b)) QT/QTc prolongation should be expected during treatment with [arsenic trioxide](#) and [torsade de pointes](#) as well as [complete heart block](#) has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with [arsenic trioxide](#) were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after [arsenic trioxide](#) infusion, and then returned towards baseline by the end of 8 weeks after [arsenic trioxide](#) infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age [499].

3.5.1.AC] Artemether

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

2)) Summary: Avoid concomitant use of [amitriptyline](#) and artemether/lumefantrine due to the additive risk of QT-interval prolongation. Coadministration of artemether/lumefantrine, a CYP2D6 inhibitor, may cause plasma concentrations of [amitriptyline](#), a CYP2D6 substrate, to significantly increase and further heighten the risk of QT-interval prolongation or other serious adverse effects. If concurrent administration of [amitriptyline](#) and artemether/lumefantrine is medically required, use caution and monitor the ECG. 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)[534].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Avoid concomitant use of [amitriptyline](#) and artemether/lumefantrine due to the additive risk of QT-interval prolongation and adverse effects. If concurrent administration of [amitriptyline](#) and artemether/lumefantrine is medically required, use caution and monitor the ECG. 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)[534].

7)) Probable Mechanism: additive effects on QT-interval prolongation; inhibition of CYP2D6-mediated metabolism of [amitriptyline](#)

3.5.1.AD] Asenapine

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

2)) Summary: Avoid using [amitriptyline](#) and asenapine concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Additionally asenapine is a weak CYP2D6 inhibitor and[974] [amitriptyline](#) is a CYP2D6 substrate [236].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Avoid using [amitriptyline](#) and asenapine concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[974].

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

3.5.1.AE] Aspirin

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.AF] [Astemizole](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of [astemizole](#) and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended[504][505].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [astemizole](#) and agents that prolong the QT interval, such as tricyclic antidepressants, is not recommended.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports

a) A comprehensive discussion of the cardiovascular effects of tricyclic antidepressants has been presented [503]. [Electrocardiogram](#) effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves.

3.5.1.AG] [Atazanavir](#)

- 1) Interaction Effect: increased plasma concentrations of tricyclic antidepressants (drowsiness, hypotension, [akathisia](#))
- 2) Summary: Coadministration of [atazanavir](#) and tricyclic antidepressants has not been studied. However, the coadministration of [atazanavir](#) and tricyclic antidepressants has the potential to produce serious and/or life-threatening adverse events[839].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: If [atazanavir](#) and tricyclic antidepressants are used concomitantly, monitor patient for clinical signs and symptoms of tricyclic antidepressant toxicity (hypotension, [akathisia](#), anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#)).

7J) Probable Mechanism: unknown

3.5.1.AH] Atomoxetine

- 1J) Interaction Effect: an increase in [atomoxetine](#) steady-state plasma concentrations
- 2J) Summary: [Atomoxetine](#) is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, [atomoxetine](#) steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as [amitriptyline](#). The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with [amitriptyline](#), the area under the concentration-time curve of [atomoxetine](#) is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than [atomoxetine](#) alone[629].
- 3J) Severity: moderate
- 4J) Onset: unspecified
- 5J) Substantiation: probable
- 6J) Clinical Management: Dosage adjustment of [atomoxetine](#) may be necessary when coadministered with [amitriptyline](#).
- 7J) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of [atomoxetine](#) by [amitriptyline](#)

3.5.1.AI] Azimilide

- 1J) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2J) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[330], [amiodarone](#) [331], [azimilide](#) [332], [bretylium](#) [333], [ibutilide](#) [334], [semitilide](#) [335], [dofetilide](#) [336], and [sotalol](#) [337]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [338][339].
- 3J) Severity: major
- 4J) Onset: rapid
- 5J) Substantiation: theoretical
- 6J) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
- 7J) Probable Mechanism: additive QT prolongation
- 8J) Literature Reports

aJ) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [328].

bJ) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetry monitoring is advised [329].

3.5.1.AJ] Azithromycin

- 1J) Interaction Effect: an increased risk of QT interval prolongation
- 2J) Summary: Use caution when using [amitriptyline](#) and [azithromycin](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].
- 3J) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [amitriptyline](#) and [azithromycin](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.AK] [Baclofen](#)

- 1) Interaction Effect: memory loss, loss of muscle tone
- 2) Summary: [Baclofen](#) when administered with antidepressants, specifically [imipramine](#), [amitriptyline](#), and [clomipramine](#), has induced [short term memory loss](#)[375]. In addition, concomitant [imipramine](#) and [baclofen](#) may result in additive muscle relaxant effects [376].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the additive effects of both drugs, monitor for excess anticholinergic activity and muscle relaxant effects with concomitant therapy.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) [Baclofen](#) when administered with antidepressants, specifically [imipramine](#), [amitriptyline](#), and [clomipramine](#), has induced [short-term memory loss](#) in three patients. Specifically, the patients could not remember [names](#) of persons or places familiar to them. The interaction is believed to be caused by [baclofen](#) enhancing the anticholinergic effects of antidepressants, which may be partially reversed by piracetam [373].

b) Concomitant [imipramine](#) and [baclofen](#) therapy has been reported to result in an additive muscle relaxant effect. A 54-year-old male with a 12-year history of [multiple sclerosis](#) and a two-year history of depression was maintained on [baclofen](#) 10 mg four times daily. The patient experienced good relief of spasticity with this regimen and maintained sufficient muscle tone to stand. [Nortriptyline](#) 50 mg nightly was added to relieve depression. On the sixth day of therapy, the patient was no longer able to stand. [Nortriptyline](#) was withdrawn and muscle tone returned within 48 hours. Two weeks later, [imipramine](#) 75 mg daily was given to the patient for treatment of depression, however, the patient again experienced loss of muscle tone. Muscle tone returned within two days of [imipramine](#) discontinuation. The additive effect between [baclofen](#) and the tricyclic antidepressants is attributed to an interaction affecting the neurotransmitters at the presynaptic membrane [374].

3.5.1.AL] [Belladonna](#)

- 1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
- 2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, [atropine](#), and [scopolamine](#) with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots[295]. Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepressants is unknown. Caution is advised.
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical

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

7) Probable Mechanism: additive anticholinergic effect

3.5.1.AM] [Belladonna Alkaloids](#)

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

2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, [atropine](#), and [scopolamine](#) with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots[295]. Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepressants is unknown. Caution is advised.

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

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

7) Probable Mechanism: additive anticholinergic effect

3.5.1.AN] [Benzphetamine](#)

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[721].

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[721].

7) Probable Mechanism: additive serotonergic effect

3.5.1.AO] [Bepridil](#)

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

2) Summary: The concomitant use of [bepridil](#) with drugs that cause QT-interval prolongation is contraindicated[559], 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[559], as coadministration may increase the risk of [ventricular arrhythmias](#).
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.AP] Bethanidine

- 1) Interaction Effect: decreased antihypertensive effectiveness
- 2) Summary: Tricyclic antidepressants inhibit the uptake of bethanidine at its site of action in the adrenergic neuron. The antagonism may last for several days after discontinuation of the antidepressant[601][602][603].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: The combination of bethanidine and [amitriptyline](#), as well as other tricyclic antidepressant agents, should be avoided. An alternative antihypertensive agent should be considered if discontinuation of [amitriptyline](#) is not appropriate.
- 7) Probable Mechanism: decreased uptake of bethanidine into adrenergic neurons
- 8) Literature Reports

a) Two of 8 adult hypertensive patients who received bethanidine or debrisoquine concurrently with a tricyclic antidepressant reported adequate control of [hypertension](#). In 24 control patients given the same drugs without antidepressants, blood pressure control was achieved in 18. Withdrawal of antidepressant therapy in several patients resulted in postural hypotension that necessitated a reduction in dosage of bethanidine or debrisoquine [600].

3.5.1.AQ] [Bretylium](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[330], [amiodarone](#) [331], azimilide [332], [bretylium](#) [333], [ibutilide](#) [334], sematilide [335], [dofetilide](#) [336], and [sotalol](#) [337]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [338][339].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [328].

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at

least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised [329].

3.5.1.AR] Bromazepam

- 1) Interaction Effect: increased risk of respiratory or cardiovascular depression
- 2) Summary: Concomitant use of bromazepam with another CNS depressant should be avoided due to increased risk for respiratory or cardiovascular depression and profound sedation[187].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of bromazepam, which is a CNS depressant, with another CNS depressant may result in respiratory or cardiovascular depression and profound sedation. Due to the added CNS depressant effects, avoid use of bromazepam and other CNS depressants[187].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AS] Bromfenac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.AT] Bromopride

- 1) Interaction Effect: potentiation of sedative effects
- 2) Summary: Potentiation of sedative effects may occur with concomitant use of bromopride and sedatives. Avoid concomitant use[230].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of bromopride with sedatives. Additive sedation may occur with concomitant use[230].
- 7) Probable Mechanism: unknown

3.5.1.AU] 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[230].
- 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[230].
- 7) Probable Mechanism: additive extrapyramidal side effects

3.5.1.AV] Brompheniramine

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[236], and [brompheniramine](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [brompheniramine](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, and diarrhea), and mental status changes (eg, 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 [240].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [brompheniramine](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.AW] Buprenorphine

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.AX] [Buprenorphine](#)

- 1)) Interaction Effect: increased risk of [respiratory depression](#)
- 2)) Summary: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[130][131] and monitor for signs of [respiratory depression](#), sedation, and hypotension [130].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[130][131] and monitor for signs of [respiratory depression](#), sedation, and hypotension [130].
- 7)) Probable Mechanism: additive [respiratory depression](#)

3.5.1.AY] [Bupropion](#)

- 1)) Interaction Effect: increased exposure of CYP2D6 substrates; increased risk of seizure
- 2)) Summary: Extreme caution is advised with concomitant use of [buPROPion](#) and other drugs that may lower the seizure threshold as this may increase the risk for seizures. Additionally, concurrent administration of [buPROPion](#) (a CYP2D6 inhibitor) and a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. The CYP2D6 substrate should be initiated at the lower end of the dose range and titrated gradually. If [buPROPion](#) is added to an existing regimen with a CYP2D6 substrate, consider decreasing the substrate dose, especially if it has a narrow therapeutic index. Use a low initial dose of [buPROPion](#) and titrate slowly to reduce the risk of seizures[303].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Extreme caution is advised with concomitant use of [buPROPion](#) and other drugs that may lower the seizure threshold as this may increase the risk for seizures. Additionally, concurrent administration of [buPROPion](#) (a CYP2D6 inhibitor) and a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. The CYP2D6 substrate should be initiated at the lower end of the CYP2D6 substrate dose range and titrated gradually. If [buPROPion](#) is added to an existing regimen with a CYP2D6 substrate, consider decreasing the CYP2D6 substrate dose, especially if it has a narrow therapeutic index. Use a low initial dose of [buPROPion](#) and titrate slowly to reduce the risk of seizures[303].
- 7)) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of CYP2D6 substrates by [buPROPion](#); lowered seizure threshold
- 8)) Literature Reports

a)) The concomitant administration of [fluoxetine](#) and [buPROPion](#) was associated with a hyperactive libido in a patient receiving treatment for [major depression](#). The patient, a 35-year-old woman, initially received treatment with [fluoxetine](#) 40 mg daily after converting from

clomipramine therapy due to suboptimal therapeutic effect. She experienced a diminished libido from the onset of clomipramine therapy which did not resolve after conversion to fluoxetine. Three months after the conversion to fluoxetine, buPROPion 100 mg/day was added to her treatment regimen as a potential antidote for the sexual dysfunction. Sexual function appeared to normalize 1 month after the start of buPROPion therapy. Approximately 5 months after beginning buPROPion, the patient complained of having an exaggerated increase in libido, causing her to discontinue all medications. Her libido returned to normal within 2 months of stopping all medication, accompanied by a recurrence of depressive symptoms. Fluoxetine was reintroduced within the same time period, producing another reduction in libido yet accompanied by a full remission from depressive symptoms [304].

b)) Coadministration of buPROPion 150 mg twice daily and a single dose of desipramine 50 mg (a CYP2D6 substrate) in healthy volunteers who were extensive CYP2D6 metabolizers (n=15) resulted in a 2-fold and 5-fold increase in desipramine Cmax and AUC respectively. The effect persisted for 7 days following the last dose of buPROPion [305].

3.5.1.AZ] 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[984][985][986]. 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[984][985][986].
- 7)) Probable Mechanism: additive effects on the QT interval

3.5.1.BA] Buspirone

- 1)) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2)) Summary: Both amitriptyline, a serotonin reuptake inhibitor[236], and busPIRone affect the serotonergic neurotransmitter systems. Serotonin syndrome has been associated with busPIRone use during postmarketing surveillance [961]. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of serotonin syndrome. Monitoring for signs and symptoms of serotonin syndrome during treatment may be warranted if amitriptyline and busPIRone are used concurrently. Symptoms of serotonin syndrome include neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (eg, 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 [240].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [busPIRone](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236][961]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

3.5.1.BB] [Butabarbital](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[142][143][144][145][146].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [133][134][135][136][137].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [138]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [139]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [140]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [141].

3.5.1.BC] [Butabarbital](#)

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls

[887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BD] [Butalbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[142][143][144][145][146].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [133][134][135][136][137].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [138]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [139]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [140]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [141].

3.5.1.BE] [Butalbital](#)

- 1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
- 2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
- 7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of **desipramine** (100 mg) were studied in eight epileptic patients chronically treated with **phenobarbital** and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma **desipramine** concentrations (74 nmol/L vs. 107 nmol/L), smaller **desipramine** area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter **desipramine** elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BF] Butorphanol

1) Interaction Effect: additive **respiratory depression**

2) Summary: Concomitant use of opioid pain or **cough** medicines and benzodiazepines may result in profound sedation, **respiratory depression**, coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for **respiratory depression** and sedation. Avoid concomitant use of prescription opioid **cough** medications with CNS depressants [126].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for **respiratory depression** and sedation. Avoid concomitant use of prescription opioid **cough** medications with CNS depressants [126].

7) Probable Mechanism: additive CNS depression

8) Literature Reports

a) Concomitant **propoxyphene** (65 mg every 6 hours) and **alprazolam** (1 mg) therapy increased the half-life of **alprazolam** by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.BG] Carbamazepine

1) Interaction Effect: decreased **amitriptyline** effectiveness

2) Summary: The concomitant use of **carbamazepine** and antidepressants has been reported to decrease antidepressant levels[561][562].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for clinical efficacy of the **amitriptyline** therapy and for any signs of toxicity of **carbamazepine**. Serum levels of both agents should be considered when either agent is added or discontinued, with appropriate dosage adjustments made accordingly.

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

8) Literature Reports

a)) A study examined the effect of [carbamazepine](#) on [amitriptyline](#) levels in 8 psychiatric inpatients treated with an average [amitriptyline](#) dosage of 137.5 mg daily. All patients were treated for a minimum of 7 days prior to measurement of baseline antidepressant concentrations. [Carbamazepine](#) was added in a mean dose of 593 mg continued over a 4 week period. In patients receiving combination therapy, serum [amitriptyline](#) and [nortriptyline](#) concentrations were significantly lower (42% and 40% respectively) than in patients receiving [amitriptyline](#) alone, although the ratio of [amitriptyline](#) to [nortriptyline](#) remained relatively unchanged [560].

3.5.1.BH] [Carbinoxamine](#)

- 1)) Interaction Effect: additive CNS effects
- 2)) Summary: Avoid concurrent use of [carbinoxamine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives, as this may cause additive CNS effects[188][189]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [carbinoxamine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may have additive effects and is therefore not recommended[188][189]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.
- 7)) Probable Mechanism: additive effects on the CNS

3.5.1.BI] [Carisoprodol](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[216][217][218][219].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7)) Probable Mechanism: CNS depression

3.5.1.BJ] [Celecoxib](#)

- 1)) Interaction Effect: an increased risk of bleeding
- 2)) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: established
- 6)) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.BKJ [Chloral Hydrate](#)

1J) Interaction Effect: additive [respiratory depression](#)

2J) Summary: [Chloral hydrate](#), with a limited therapeutic index, can produce acute intoxication and [respiratory depression](#)[203]. When used in combination with benzodiazepines, these drugs may have additive CNS and respiratory depressant effects.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7J) Probable Mechanism: CNS depression

3.5.1.BLJ [Chloral Hydrate](#)

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

2J) Summary: [Chloral hydrate](#) and tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose[324][325]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concurrent administration of [chloral hydrate](#) and a tricyclic antidepressant is not recommended.

7J) Probable Mechanism: additive effects on QT prolongation

3.5.1.BMJ [Chloroquine](#)

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

2J) Summary: [Chloroquine](#) can prolong the QT interval in some patients, which may result in [ventricular tachycardia](#), [ventricular fibrillation](#), and [torsades de pointes](#). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [chloroquine](#) and tricyclic antidepressants is not recommended[641][642].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concurrent administration of [chloroquine](#) and a tricyclic antidepressant is not recommended.

7J) Probable Mechanism: additive effects on QT prolongation

3.5.1.BN] Chlorotrianisene

1J) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2J) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[550], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [551]. The effects of the interaction appear to be estrogen dose-related [552] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [553].

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7J) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic

8J) Literature Reports

aJ) A study evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 mg daily) and placebo, five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (50 mcg daily), while five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after two weeks, the five patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received [imipramine](#) 150 mg and [ethinyl estradiol](#) 50 mcg daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [541].

bJ) A case reported by [542] demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 mg and [imipramine](#) 100 mg. The patient developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [543].

cJ) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [544].

d)) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 mg at bedtime while 19 took [clomipramine](#) 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [545].

e)) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 mg daily for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 mg daily for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 mg was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogen](#) 1.25 mg daily who was prescribed [amitriptyline](#) 50 mg daily for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogen](#) 1.25 mg daily and [amitriptyline](#) 50 mg daily. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [546].

f)) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 mcg or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [547].

g)) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [548]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [549].

3.5.1.BO| [Chlorpheniramine](#)

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

2)) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[236], and [chlorpheniramine](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [chlorpheniramine](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, and diarrhea), and mental status changes (eg, 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 [240].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [chlorpheniramine](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. If coadministration is required, appropriate monitoring may be warranted.

7J) Probable Mechanism: additive serotonergic effect

3.5.1.BP| Chlorpromazine

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

2J) Summary: Use caution when using [amitriptyline](#) and [chlorproMAZINE](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when using [amitriptyline](#) and [chlorproMAZINE](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].

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

3.5.1.BQ| Chlorzoxazone

1J) Interaction Effect: additive [respiratory depression](#)

2J) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[216][217][218][219].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7J) Probable Mechanism: CNS depression

3.5.1.BR| Choline Salicylate

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.BS] Cimetidine

- 1) Interaction Effect: [chlordiazepoxide](#) toxicity (CNS depression)
- 2) Summary: [Cimetidine](#) decreases the clearance of benzodiazepines that are metabolized by hydroxylation or dealkylation (eg, [diazepam](#), [chlordiazepoxide](#), [clorazepate](#), [flurazepam](#), [prazepam](#), [halazepam](#), [alprazolam](#), [triazolam](#), [midazolam](#), [quazepam](#), [estazolam](#), [bromazepam](#)) [149][150][151][152]. Adverse effects such as pronounced sedation and impaired cognitive and psychomotor function have been reported [153][154]. Benzodiazepines for which nitroreduction is a prominent metabolic pathway might also have their clearance decreased by [cimetidine](#) (eg, [nitrazepam](#), [clonazepam](#)) [155][156]. Those benzodiazepines eliminated primarily by glucuronidation do not interact with [cimetidine](#) (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)) [157][158][159][160].
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce benzodiazepine dose or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).
- 7) Probable Mechanism: decreased [chlordiazepoxide](#) metabolism
- 8) Literature Reports

a) [Chlordiazepoxide](#) pharmacokinetics was studied in eight normal patients before and after one week of [cimetidine](#) 300 mg four times daily. The clearance of [cimetidine](#) was reduced 64%. [Chlordiazepoxide](#) pharmacokinetics were studied in seven healthy patients after [cimetidine](#) administration 300 mg four times daily for one day, 30 days, and 48 hours after discontinuing [cimetidine](#) [147]. [Chlordiazepoxide](#) plasma clearance was reduced 54% after one day of [cimetidine](#), 57% after 30 days of [cimetidine](#), and returned to normal 48 hours after discontinuing [cimetidine](#) [148].

3.5.1.BT] Cimetidine

- 1) Interaction Effect: [amitriptyline](#) toxicity (dry mouth, blurred vision, urinary retention)
- 2) Summary: [Cimetidine](#) decreases the metabolism and increases the serum level of [amitriptyline](#) [626][627][628]. If concurrent administration is necessary, lower than usual [amitriptyline](#) doses may be required. Serum [amitriptyline](#) levels may be considered within the few first days of starting or discontinuing [cimetidine](#) [236].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent administration of [amitriptyline](#) and [cimetidine](#) may increase the exposure of [amitriptyline](#). If coadministration is required, lower than usual [amitriptyline](#) doses may be required. Serum [amitriptyline](#) levels may be considered within the few first days of starting or discontinuing [cimetidine](#) [236]. An alternative H₂ blocker that does not appear to impair the metabolism of [amitriptyline](#), such as [ranitidine](#) or [famotidine](#), might be considered.
- 7) Probable Mechanism: decreased [amitriptyline](#) metabolism

3.5.1.BU] Cinacalcet

- 1) Interaction Effect: increased exposure of [amitriptyline](#)

2) Summary: Concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#). Poor metabolizers are especially at risk. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and adjust the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#), especially in poor metabolizers. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and reduce the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].

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

3.5.1.BV] [Ciprofloxacin](#)

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

2) Summary: Use caution when using [amitriptyline](#) and [ciprofloxacin](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236][277].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when using [amitriptyline](#) and [ciprofloxacin](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236][277].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BW] [Cisapride](#)

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

2) Summary: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[630].

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](#)[630].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.BX] [Citalopram](#)

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

2) Summary: Concomitant use of [amitriptyline](#) and [citalopram](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant use 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[275]. Additionally, caution is advised when using [amitriptyline](#), a CYP2D6 substrate, with a CYP2D6 inhibitor, such as [citalopram](#), as lower doses of [amitriptyline](#) and/or [citalopram](#) may be required.

It is desirable to monitor [amitriptyline](#) concentrations whenever a CYP2D6 inhibitor is used concurrently [236].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [amitriptyline](#) and [citalopram](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant use 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[275]. Additionally, caution is advised when using [amitriptyline](#), a CYP2D6 substrate, with a CYP2D6 inhibitor, such as [citalopram](#). Consider monitoring [amitriptyline](#) concentrations and lower doses of [amitriptyline](#) and/or [citalopram](#) may be required [236].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BY] [Clarithromycin](#)

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

2) Summary: Use caution with coadministration of [clarithromycin](#) with other selected QT-prolonging agents, as additive prolongation effects on the QT interval may occur[533].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of [clarithromycin](#) with other selected QT-prolonging agents, as additive prolongation effects on the QT interval may occur[533].

7) Probable Mechanism: additive prolongation effects on QT interval

3.5.1.BZ] [Clobazam](#)

1) Interaction Effect: increased exposure of [amitriptyline](#)

2) Summary: Concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#). Poor metabolizers are especially at risk. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and adjust the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#), especially in poor metabolizers. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and reduce the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].

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

3.5.1.CA] [Clomipramine](#)

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

2) Summary: Concomitant use of [amitriptyline](#) and [clomiPRAMINE](#) is not common clinical practice. However if using [amitriptyline](#) and [clomiPRAMINE](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236]. Additionally, caution is advised when using [amitriptyline](#), a CYP2D6 substrate, with [clomiPRAMINE](#),

a CYP2D6 substrate and inhibitor. Consideration should be given to monitoring both [amitriptyline](#) and [clomiPRAMINE](#) levels [239][236].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [amitriptyline](#) and [clomiPRAMINE](#) is not common clinical practice. However if using [amitriptyline](#) and [clomiPRAMINE](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236]. Additionally, caution is advised when using [amitriptyline](#), a CYP2D6 substrate, with [clomiPRAMINE](#), a CYP2D6 substrate and inhibitor. Monitoring of both [amitriptyline](#) and [clomiPRAMINE](#) levels should be considered [239][236].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.CB| [Clonidine](#)

1) Interaction Effect: decreased antihypertensive effectiveness

2) Summary: Concomitant [clonidine](#) and tricyclic antidepressant (TCA) therapy may impair the antihypertensive effects of [clonidine](#)[490]. Tricyclic antidepressants increase the release of noradrenaline, presumably through re-uptake blockade. [Clonidine](#) reduces the release of noradrenaline by stimulating pre-synaptic alpha-2 adrenoreceptors, whose function is to inhibit noradrenaline release [491][492][493][494]. Mianserin, a tetracyclic antidepressant, was not shown to exhibit the impairment of [clonidine's](#) antihypertensive effects seen with tricyclic antidepressants [495][496].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response. Higher doses of [clonidine](#) may be required. An alternative class of antihypertensive agents or an alternative class of antidepressants might be considered.

7) Probable Mechanism: pharmacological antagonism at central alpha-2 receptors

8) Literature Reports

a) One case report describes prolonged [clonidine](#) withdrawal syndrome in a patient where [clonidine](#) and [amitriptyline](#) were withdrawn simultaneously. Prior to [jejunal resection](#) surgery, [clonidine](#) (0.1 mg twice daily) and [amitriptyline](#) (25 mg four times daily) and other medications were discontinued in a 73-year-old female. After surgery, the patient experienced elevated arterial blood pressure (220/70 to 210/90), [tachycardia](#) (95 to 105) and extreme anxiety. Treatment with [methyldopa](#) and [propranolol](#) reversed symptoms after therapy for four days. Anxiety has been reported after withdrawal of antidepressants. [Tachycardia](#) and [hypertension](#) are the features of a well-described [clonidine](#) withdrawal syndrome. The persistence of this syndrome in this patient may have been due to the long-term catecholamine increases seen in patients on antidepressant therapy [486].

b) The interaction between [clonidine](#) and [desipramine](#) has been studied in five hypertensive patients. The results of this double-blind placebo controlled study showed that the introduction of the tricyclic antidepressant led to the loss of blood pressure control in four of the five subjects within two weeks. The rise in the arterial pressure was more prominent in the supine position than in the erect. The average blood pressure increase in the [desipramine](#) period compared to the placebo period was 22/15 mm Hg in the lying position and 12/11 mm Hg standing [487].

c) A study enrolled eleven drug-free patients who met the Research Diagnostic Criteria for [Major Depressive Disorder](#) in a study to determine the effects of [desipramine](#) on central

adrenergic function. Patients were given a [clonidine](#) infusion after 0, 1 and 3 weeks of treatment with [desipramine](#). Results showed that the sedative and hypotensive effects of [clonidine](#) were significantly inhibited after three weeks of treatment with [desipramine](#). This interaction was also seen at one week, but did not reach clinical significance. The authors concluded that the effects that were observed during the study were due to an acute drug effect, rather than to a chronic adaptive change [488].

d)) One case report describes a 65-year-old man who was experiencing perineal pain following the excision of a [carcinoma](#). Pain management of [amitriptyline](#) 75 mg nightly and sodium [valproate](#) 500 mg three times daily was initiated after slow-release [morphine](#) only had a limited effect. A [clonidine](#) spinal [intrathecal injection](#) of 75 micrograms was given when it was felt that the patient had become tolerant to opioid treatment. Within five minutes, the patient was found to be in severe pain, which resolved within 30 minutes after diamorphine was given. Two mechanisms for this interaction were postulated. In the first, the pain could have been the result of a clonidine-cholinergic interaction. In the second, the tricyclic augmentation of serotonergic transmission may have unmasked an effect of [clonidine](#) at central receptors to enhance nociception [489].

3.5.1.CC] Clonixin

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: unknown

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.CD] Clorgyline

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

2)) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[594][595][596][597]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [598]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [599].

3)) Severity: contraindicated

- 4) Onset: delayed
- 5) Substantiation: established
- 6) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.
- 7) Probable Mechanism: altered catecholamine uptake and metabolism
- 8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [575][576][577][578][579][580]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [581].

b) The development of [serotonin syndrome](#) was reported due to administration of a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [582].

c) A drug interaction was reported when a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [583].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [584].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [585].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranlycypromine](#) in a physically healthy 34-year old man. After taking several doses, the patients developed

symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to [disseminated intravascular coagulation](#) and eventual death [586].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranylcypromine](#) in any combination, and d) close monitoring of patients [587][577][578][588][589]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [590]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added [591]. Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [590]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [592][578][593].

3.5.1.CE] [Clozapine](#)

- 1)** Interaction Effect: increased plasma levels of [clozapine](#), other CYP2D6 substrates, or both
- 2)** Summary: Concomitant use of [clozapine](#), a CYP2D6 substrate, with other drugs metabolized by CYP2D6 can increase plasma levels of one or both CYP2D6 substrates. Use caution with concomitant use of [clozapine](#) and other drugs metabolized by CYP2D6. Lower doses than usually prescribed for either [clozapine](#) or other CYP2D6 substrates may be required[631]. Monitor for increased CYP2D6-mediated adverse effects.
- 3)** Severity: moderate
- 4)** Onset: unspecified
- 5)** Substantiation: theoretical
- 6)** Clinical Management: Use caution with concomitant use of [clozapine](#) and other drugs metabolized by CYP2D6. Lower doses than usually prescribed for either [clozapine](#) or other CYP2D6 substrates may be required[631]. Monitor for increased CYP2D6-mediated adverse effects.
- 7)** Probable Mechanism: competitive substrate inhibition
- 8)** Literature Reports

a) [Paroxetine](#) had no significant effect on serum levels of [clozapine](#) in 14 patients with [schizophrenia](#). [Clozapine](#) 2.5 to 3 mg/kg/day was given for 14 days, then [paroxetine](#) 20 mg daily was added for 14 days. Serum concentrations of [clozapine](#) and 2 metabolites were measured on days 1, 7, and 14. Over the course of this study there was no significant difference in serum concentrations of [clozapine](#) or its metabolites [632].

b) Serum concentrations of [clozapine](#) and noreclozapine, the major metabolite, were evaluated when given in combination with the SSRIs [fluoxetine](#), [paroxetine](#), and [sertraline](#). Eighty outpatients receiving [clozapine](#) all had been diagnosed with [schizophrenia](#) or major affective disorder, and 40 of these patients were receiving an SSRI in combination with [clozapine](#). Of these 40 patients, 14 were receiving [fluoxetine](#), 10 were receiving [sertraline](#), and 16 were receiving [paroxetine](#) therapy. Among the patients on SSRI therapy, serum concentrations of [clozapine](#) and noreclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of [clozapine](#) plus noreclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating [clozapine](#) impaired clearance. The differences between the 3 SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs [633].

3.5.1.CF| Cobicistat

- 1) Interaction Effect: increased exposure of [amitriptyline](#)
- 2) Summary: Concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#). Poor metabolizers are especially at risk. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and adjust the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#), especially in poor metabolizers. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and reduce the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amitriptyline](#)

3.5.1.CG| Cocaine

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[236], and cocaine affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and cocaine are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, and diarrhea), and mental status changes (eg, 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 [240].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and cocaine, as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.CH| Codeine

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].

7) Probable Mechanism: additive CNS depression

8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.CI) [Conjugated Estrogens](#)

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[997], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [998]. The effects of the interaction appear to be estrogen dose-related [999] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [1000].

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 mg daily) and placebo, five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (50 mcg daily), while five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after two weeks, the five patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received [imipramine](#) 150 mg and [ethinyl estradiol](#) 50 mcg daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [988].

b) A 32-year-old female taking [conjugated estrogens](#) 2.5 mg and [imipramine](#) 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant

headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [989] [990].

c) In a study women received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [991].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 mg at bedtime while 19 took [clomipramine](#) 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [992].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 mg daily for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 mg daily for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 mg was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogen](#) 1.25 mg daily who was prescribed [amitriptyline](#) 50 mg daily for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogen](#) 1.25 mg daily and [amitriptyline](#) 50 mg daily. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [993].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 mcg or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [994].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [995]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [996].

3.5.1.CJ] 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[356]. 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[356]. Dose reduction of crizotinib may be warranted.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.CK] [Cyclobenzaprine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: [Serotonin syndrome](#), a life-threatening condition, has occurred with coadministration of [cyclobenzaprine](#) with other drugs, such as a tricyclic antidepressants (TCAs). 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[434][435].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [cyclobenzaprine](#) with a tricyclic antidepressant (TCA) 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[434][435].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.CL] [Dabrafenib](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Dabrafenib, as a single agent, has potential to prolong the QT interval; therefore, concomitant use with other drugs that can prolong the QT interval may cause additive effects on the QT interval[858]. Therefore, caution should be exercised with concomitant use and consider assessment and periodic monitoring for [ventricular arrhythmia](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of dabrafenib with other drugs that cause QT-interval prolongation may result in additive effects on the QT interval[858]. Exercise caution with concomitant use and consider assessment and periodic monitoring for [ventricular arrhythmia](#).
- 7) Probable Mechanism: additive QT prolongation

3.5.1.CM] [Dantrolene](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[216][217][218][219].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.CN| [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[645][646].
- 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[645][646].
- 7) Probable Mechanism: unknown

3.5.1.CO| [Dasatinib](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [amitriptyline](#) and [dasatinib](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[297].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [amitriptyline](#) and [dasatinib](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[297].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.CP| [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[984][985][986]. 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[984][985][986].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.CQ| 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[462].
- 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[462].
- 7) Probable Mechanism: additive QT- interval prolongation

3.5.1.CR| Desipramine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [amitriptyline](#) and [desipramine](#) is not common clinical practice. However if using [amitriptyline](#) and [desipramine](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [amitriptyline](#) and [desipramine](#) is not common clinical practice. However if using [amitriptyline](#) and [desipramine](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.CS| Deslorelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[984][985][986]. 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[984][985][986].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.CT| Desogestrel

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2j) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3j) Severity: minor

4j) Onset: delayed

5j) Substantiation: probable

6j) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7j) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8j) Literature Reports

aj) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

bj) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

cj) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d)) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e)) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f)) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g)) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.CU] Desvenlafaxine

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

2)) Summary: Coadministration of desvenlafaxine, a weak CYP2D6 inhibitor and serotonergic drug, with another serotonergic agent that is also a CYP2D6 substrate may result in increased drug exposure and increased risk of [serotonin syndrome](#). [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy. If concomitant use is required, no dose adjustment of the CYP2D6 substrate is needed with concurrent desvenlafaxine 100 mg/day or less. Reduce the CYP2D6 substrate dose by 50% if using concurrently with desvenlafaxine 400 mg/day (unapproved dosing) and increase the CYP2D6 substrate to the original dose if concurrent desvenlafaxine 400 mg/day is discontinued. Monitor all patients closely for signs and symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases of either drug[391].

3)) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution with coadministration of desvenlafaxine (a weak CYP2D6 inhibitor and serotonergic agent) with serotonergic drugs that are also CYP2D6 substrates. Coadministration may result in additive serotonergic effects and may increase CYP2D6 substrate exposure. If concurrent use is required, CYP2D6 substrates may be given at the recommended dose when coadministered with desvenlafaxine 100 mg/day or less. Reduce the CYP2D6 substrate dose by 50% if using concurrently with desvenlafaxine 400 mg/day (unapproved dosing); increase the CYP2D6 substrate to the original dose if concurrent desvenlafaxine 400 mg/day is discontinued. Careful monitoring for signs and symptoms of [serotonin syndrome](#) is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops[391].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by desvenlafaxine; additive serotonergic effect
- 8) Literature Reports

a) Coadministration of [desipramine](#) (a CYP2D6 substrate) 50 mg with desvenlafaxine 400 mg/day (unapproved dosing) in a clinical study resulted in an increase of approximately 50% for the C_{max} and 90% for the AUC of [desipramine](#). The differences in [desipramine](#) metabolism were not considered clinically relevant when the dose of desvenlafaxine was 100 mg/day (25% increase in C_{max} and 17% in AUC) [391].

3.5.1.CV] Dexibuprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.CW] Dextketoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436].

When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.CX] [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[721].

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[721].

7) Probable Mechanism: additive serotonergic effect

3.5.1.CY] [Dextromethorphan](#)

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

2) Summary: The concomitant use of [dextromethorphan](#) and a tricyclic antidepressant (such as [amitriptyline](#)) may result in an increased risk of [serotonin syndrome](#). While not specifically studied with [amitriptyline](#), the concomitant use of [desipramine](#) 25 mg (another tricyclic antidepressant), with the combination [dextromethorphan](#) 30 mg/[quinidine](#) 30 mg resulted in an approximately 8-fold increase in steady state [desipramine](#) levels compared to administration of [desipramine](#) alone[987]. If both [amitriptyline](#) and [dextromethorphan](#) are used concurrently, monitor for signs and symptoms of [serotonin syndrome](#) (eg, altered mental status, [hypertension](#), restlessness, myoclonus, [hyperthermia](#), hyperreflexia, diaphoresis, shivering, and tremor).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [dextromethorphan](#) to patients who are taking a tricyclic antidepressant (such as [amitriptyline](#)), as concomitant use may result in an increased risk of [serotonin syndrome](#)[987].

7) Probable Mechanism: additive CNS serotonin concentrations

3.5.1.CZ] [Diazepam](#)

1) Interaction Effect: psychomotor deficits (decreased reaction time, decreased vigilance)

2) Summary: A controlled study observed that coadministration of [diazepam](#) with [amitriptyline](#) resulted in additive deficits in several psychomotor tests[428]. The potential interaction between [diazepam](#) and [amitriptyline](#) was studied in four depressed patients receiving 75 to 150 mg daily of [amitriptyline](#) and 10 to 15 mg daily of [diazepam](#) [429]. Researchers were unable to demonstrate any change in blood levels of [amitriptyline](#) or [nortriptyline](#). Additional controlled studies or case reports are necessary to determine the degree of impairment resulting from coadministration of these two agents.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: If coadministration of [amitriptyline](#) with [diazepam](#) is necessary, patients should be warned that they may experience additive [psychomotor impairment](#) that may affect driving or other tasks requiring complex motor skills.

7) Probable Mechanism: additive psychomotor deficits

8) Literature Reports

a) In a controlled study of performance of 90 healthy volunteers, the effects of [fluoxetine](#), [amitriptyline](#), or placebo on [diazepam](#) were studied. Volunteers received one of six treatment combinations, and were given performance tests including a critical tracking test, divided attention test, visual search task, memory test, and vigilance test. [Fluoxetine](#) alone did not affect performance, but when [fluoxetine](#) was added to [diazepam](#), there was a significant increase in the divided attention tracking error and significant impairment on the vigilance test. For [amitriptyline](#) alone and during coadministration with [diazepam](#) significant impairment was observed. On most tests, the combination of [amitriptyline](#) and [diazepam](#) resulted in additive effects. The authors concluded that the combination of [diazepam](#) and an antidepressant may increase an individual's risk during driving and while performing other complex tasks [427].

3.5.1.DA] [Diclofenac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.DB| Dicumarol

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[450][451]. Considerable interindividual differences may be found [452].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: In patients receiving oral [anticoagulant therapy](#), the prothrombin time ratio or INR ([international normalized ratio](#)) should be closely monitored with the addition and withdrawal of treatment with [amitriptyline](#), and should be reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in order to maintain the desired level of [anticoagulation](#).
- 7) Probable Mechanism: decreased dicumarol metabolism; increased dicumarol absorption
- 8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of [nortriptyline](#) or [amitriptyline](#) resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects [447]. This effect was not observed with [warfarin](#).

b) A single oral dose of bishydroxycoumarin after eight days of [nortriptyline](#) resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in six healthy volunteers [448]. The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term [anticoagulant therapy](#) who used concurrent TCAs [449]. TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.DC| [Dienestrol](#)

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[387], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [388]. The effects of the interaction appear to be estrogen dose-related [389] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [390].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical

6j) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7j) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic.

8j) Literature Reports

aj) A study evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [378].

bj) A case reported by [379] demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [380].

cj) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [381].

dj) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [382].

ej) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and

a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [383].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [384].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [385]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [386].

3.5.1.DD] Dienogest

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was

drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b)) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c)) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d)) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e)) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f)) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.DE] **Diethylstilbestrol**

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, **akathisia**)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[406], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [407]. The effects of the interaction appear to be estrogen dose-related [408] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on **estrogen therapy** [409].

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic

8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received **imipramine** (150 milligrams/day) and placebo, 5 patients received **imipramine** (150 milligrams/day) and **ethinyl estradiol** (50 micrograms/day), while 5 patients received **imipramine** (150 milligrams/day) and **ethinyl estradiol** (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and **imipramine** demonstrated a significantly greater improvement in symptoms than did the 10 patients taking **imipramine** alone. However, after 2 weeks, the 5 patients that received **imipramine** and high-dose estrogen had not improved as much as the patients receiving **imipramine** and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking **imipramine**. Following the discontinuation of **ethinyl estradiol**, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received **imipramine** 150 milligrams and **ethinyl estradiol** 50 micrograms daily did not improve as much as 10 patients receiving only **imipramine**. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [397].

b) A case reported by [398] demonstrated an interaction in a 32-year-old female taking **conjugated estrogens** 2.5 milligrams and **imipramine** 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [399].

c) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [400].

d) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [401].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogen](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogen](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [402].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [403].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [404]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [405].

3.5.1.DF] [Diflunisal](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.DG| [Dihydrocodeine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.DH| [Diphenhydramine](#)

- 1) Interaction Effect: increased anticholinergic effects (dry mouth, urinary retention)
- 2) Summary: Concomitant antidepressants with strong anticholinergic effects (eg, [amitriptyline](#), [trimipramine](#), [amoxapine](#), [doxepin](#), [imipramine](#), [nortriptyline](#), [maprotiline](#)) and antihistamines may increase the possibility of [adynamic ileus](#), urinary retention, or chronic [glaucoma](#). This interaction may be more prominent in elderly patients[840].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Patients should be warned that taking antihistamines, including over-the-counter sleeping pills and cold and allergy preparations, may increase the side effects of [amitriptyline](#).

Patients should be monitored for dry mouth, drowsiness, and problems with urination. Lower doses of [diphenhydrAMINE](#) should be considered.

7J) Probable Mechanism: additive anticholinergic effects

3.5.1.DIJ Dipyrrone

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.DJ Disopyramide

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

2J) Summary: Concomitant use of tricyclic antidepressants, including [amitriptyline](#), and class IA antiarrhythmics, including [disopyramide](#), may increase the risk of [cardiotoxicity](#) due to similar cardiac effects of these drugs[232][233]. Therefore, monitoring the patient for signs and symptoms of [cardiac toxicity](#) during coadministration of [amitriptyline](#) and [disopyramide](#) may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [amitriptyline](#) and [disopyramide](#) may increase the risk of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs[232][233]. Consider monitoring the patient for signs and symptoms of [cardiac toxicity](#), including any changes in the ECG.

7J) Probable Mechanism: additive [cardiac toxicity](#)

8J) Literature Reports

aJ) In a placebo controlled study, [imipramine](#) 3.5 mg/kg was administered daily to seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed [premature atrial depolarizations](#) and [premature ventricular depolarizations](#) before therapy. One patient had 33 [premature atrial depolarizations](#) (PAD) and 30 [premature ventricular depolarizations](#) (PVD) per hour, which decreased to 0.4 PAC and zero PVC per

hour on [imipramine](#). The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on [imipramine](#). The authors also cautioned that the incidence of [cardiotoxicity](#) may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that [quinidine](#) and [procainamide](#) not be used to treat the [arrhythmias](#) of a tricyclic overdose. The similarities between these agents may exacerbate the [cardiotoxicity](#) [235].

b)) An increased incidence in sudden death was observed in 6 out of 53 patients with cardiac disease receiving [amitriptyline](#), compared with 0 out of 53 in the control group. It was recommended that [amitriptyline](#) be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful [26]. Additional studies were conducted which further confirmed that [amitriptyline](#) was associated with an increased incidence of sudden death in patients with preexisting cardiac disease [430][431].

3.5.1.DK] [Disulfiram](#)

- 1)) Interaction Effect: an increased risk of [chlordiazepoxide](#) toxicity (CNS depression)
- 2)) Summary: The potential exists for increased [chlordiazepoxide](#) serum concentrations when [disulfiram](#) is given concurrently. Inhibition of hepatic metabolism of benzodiazepines that undergo oxidative metabolism is thought to be the mechanism of action[228][229].
- 3)) Severity: minor
- 4)) Onset: delayed
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Monitor for signs of benzodiazepine intoxication (e.g., sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce [chlordiazepoxide](#) dose or consider switching to a benzodiazepine eliminated by glucuronidation (e.g., [lorazepam](#), [oxazepam](#)).
- 7)) Probable Mechanism: decreased hepatic metabolism
- 8)) Literature Reports

a)) Concomitant [disulfiram](#) and benzodiazepine therapy may potentiate the sedative effects of the benzodiazepine. The metabolic clearance of various benzodiazepines when given concurrently with [disulfiram](#) was studied. Determinations of plasma [chlordiazepoxide](#) concentrations showed that the parent compound and desmethyl metabolite had a decreased plasma clearance in both healthy and alcoholic patients. The plasma clearance of [diazepam](#) decreased in both healthy and alcoholic patients by 41%. There was a corresponding decrease in the active N-desmethyl metabolites of both drugs. [Disulfiram](#) increased the half-life of [chlordiazepoxide](#) by 84% and [diazepam](#) by 37%. The disposition of [oxazepam](#) was not altered significantly by [disulfiram](#), but the half-life was increased by 17%. [Oxazepam](#) may be the drug of choice in patients on [disulfiram](#) who require benzodiazepine therapy [227].

3.5.1.DL] [Disulfiram](#)

- 1)) Interaction Effect: an increased risk of a psychotic and confusional mental state
- 2)) Summary: Concomitant [amitriptyline](#) and [disulfiram therapy](#) has been reported to result in the development of a confusional and psychotic mental state[524]. Another researcher reported that [amitriptyline](#) may potentiate the [disulfiram](#) reaction to ethanol [525]. However, this finding was disputed by [526], [527], and [528].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: theoretical

- 6) Clinical Management: Monitor the patient for evidence of deteriorating mental status.
- 7) Probable Mechanism: elevated levels of various monoamines and potentially increased [dopamine](#) levels
- 8) Literature Reports

a) Two cases of [organic brain syndrome](#) (OBS) occurred in a 33-year-old male receiving 200 mg [amitriptyline](#) nightly and [disulfiram](#), and another in a 57-year-old male receiving [amitriptyline](#) 100 mg daily [disulfiram](#) 250 mg daily. In the first case, the onset of OBS was four weeks after starting [amitriptyline](#) and seven weeks after starting [disulfiram](#). In the 57-year-old, onset of OBS occurred one week after starting [amitriptyline](#) and five weeks after starting [disulfiram](#). The first patient recovered five days after discontinuing both medications and the second patient recovered three days after stopping [disulfiram](#) and reducing the dose of [amitriptyline](#) to 50 mg daily. The mechanism appeared to be an elevation in various monoamines, potentially leading to increased [dopamine](#) levels, which is a pharmacologic effect of both drugs [523].

3.5.1.DM] [Dofetilide](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[330], [amiodarone](#) [331], azimilide [332], [bretylum](#) [333], [ibutilide](#) [334], sotalol [335], [dofetilide](#) [336], and [sotalol](#) [337]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [338][339].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [328].

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetry monitoring is advised [329].

3.5.1.DN] [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[288][289].

- 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[288][289].
- 7) Probable Mechanism: unknown; additive QT-interval prolongation

3.5.1.DO] Domperidone

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Use caution with coadministration of [amitriptyline](#), a potential QT prolonging drug, and domperidone, a drug that has been associated with an increased risk of sudden cardiac death. In case control studies, an increase 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[1006].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering [amitriptyline](#) and domperidone as this may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#) and sudden cardiac death, particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years. If coadministration is necessary, domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure[1006].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.DP] Donepezil

- 1) Interaction Effect: increased risk of QT-interval prolongation and [torsade de pointes](#)
- 2) Summary: [Donepezil](#) has been associated with QT-interval prolongation[771][772]. 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[771][772]. Use caution when administering [donepezil](#) concomitantly with other drugs that cause QT-interval prolongation
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.DQ] Dong Quai

- 1) Interaction Effect: excessive muscle relaxation and central nervous system depression
- 2) Summary: Dong quai extract inhibited metabolism of [diazepam](#) and increased its muscle relaxant effect in rats[207]. The effect of dong quai on the metabolism of [diazepam](#) and other benzodiazepines in humans is unknown, as the dose used in the animal study (1 gram/kilogram) is higher than that usually used in humans. Theoretically, if dong quai similarly affects the pharmacokinetics of benzodiazepines in

humans, increased levels of benzodiazepine may occur which may result in greater pharmacologic effect of the benzodiazepine. Furocoumarins in dong quai may be responsible for inhibition of hepatic drug metabolism through inhibition of CYP2C11- and CYP2D1-mediated demethylation, CYP3A2-mediated hydroxylation, and CYP2D1-mediated 4'-hydroxylation of [diazepam](#) [207]. It is suspected that dong quai may affect other drugs metabolized by the cytochrome P450 enzymes which metabolize [diazepam](#). Caution is advised.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Monitor patients taking dong quai and benzodiazepines concomitantly for excessive muscle relaxant and sedative effects of benzodiazepines.

7) Probable Mechanism: inhibition of hepatic cytochrome P450 enzyme metabolism of benzodiazepines

8) Literature Reports

a) Angelica dahurica (dong quai) extract 1 gram/kilogram orally increased the maximum concentration of oral [diazepam](#), yet did not alter pharmacokinetics of intravenous (IV) [diazepam](#) in rats. [Diazepam](#) 5 milligrams/kilogram (mg/kg) was administered orally to rats alone, and one hour after dong quai extract. When administered alone, only the maximum concentration (Cmax) of [diazepam](#) could be calculated, as the plasma concentration of [diazepam](#) was undetectable at all sample time points except for 2 hours. After dong quai, [diazepam](#) Cmax increased from 23.0 +/- 12.4 nanograms/milliliter (ng/mL) to 92.1 +/- 50.3 ng/mL (p less than 0.05). [Diazepam](#) pharmacokinetics were not significantly changed by dong quai when [diazepam](#) was administered intravenously. [Diazepam](#) is metabolized by CYP2C11- and CYP2D1-mediated demethylation, CYP3A2-mediated hydroxylation, and CYP2D1-mediated 4'-hydroxylation. Dong quai extract inhibited all of these isoenzymes [206].

b) Angelica dahurica (dong quai) extract 1 gram/kilogram orally significantly increased the muscle relaxant effect of [diazepam](#) (5 mg/kg IV) in rats. Duration of rotarod disruption was increased with high-dose oral dong quai (1 gram/kg) versus [diazepam](#) alone (p less than 0.05). Low-dose oral dong quai (0.3 grams/kg) had no effect on rotarod performance when administered with [diazepam](#) 5 mg/kg IV. Dong quai administered alone had no effect on rotarod performance [206].

3.5.1.DR] [Doxepin](#)

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

2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[236], and [doxepin](#) [979] affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [doxepin](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, and diarrhea), and mental status changes (eg, 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 [240].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [doxepin](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

3.5.1.DS] [Doxorubicin](#)

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

2) Summary: Avoid concurrent use of [DOXOrubicin](#), a CYP2D6 substrate, with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may occur[777]. Although no formal drug interaction studies have been done with [DOXOrubicin hydrochloride liposome](#) injection, it may interact with drugs known to interact with the conventional formulation of [DOXOrubicin](#) [778].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concurrent use of [DOXOrubicin](#) with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may result[777].

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

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

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

2) Summary: Avoid concurrent use of [DOXOrubicin](#), a CYP2D6 substrate, with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may occur[777]. Although no formal drug interaction studies have been done with [DOXOrubicin hydrochloride liposome](#) injection, it may interact with drugs known to interact with the conventional formulation of [DOXOrubicin](#) [778].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concurrent use of [DOXOrubicin](#) with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may result[777].

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

3.5.1.DU] [Doxylamine](#)

1) Interaction Effect: increased risk of CNS depression

2) Summary: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[171][172]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[171][172]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.

7) Probable Mechanism: additive CNS depression

3.5.1.DV] [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](#)[455].
- 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](#)[455].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.DW] [Droperidol](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Droperidol](#) has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of [droperidol](#) and other drugs known to prolong the QTc interval, including tricyclic antidepressants is not recommended[536][537].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [droperidol](#) and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive cardiac effects

3.5.1.DX] [Drospirenone](#)

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes
- 8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of

the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after

taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.DY] Droxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.DZ] Duloxetine

1) Interaction Effect: increased exposure of [amitriptyline](#)

2) Summary: Concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#). Poor metabolizers are especially at risk. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and adjust the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#), especially in poor metabolizers. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma

levels of [amitriptyline](#) and reduce the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].

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

3.5.1.EA] [Efavirenz](#)

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

2J) Summary: Consider alternatives to [efavirenz](#) when used concomitantly with another drug that prolongs the QT interval or has a known risk of [torsade de pointes](#), because additive effects on the QT interval may occur. In a QT study of 58 healthy subjects, the mean C_{max} in patients with the CYP2B6 *6/*6 genotype was 2.25-fold higher than the mean C_{max} in those with the CYP2B6 *1/*1 genotype and the mean QTc interval prolongation was 8.7 milliseconds in subjects with the CYP2B6 *6/*6 genotype[358].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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[358].

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

8J) Literature Reports

aJ) In a QT study of healthy subjects (N=58) enriched for CYP2B6 polymorphisms, a positive association between [efavirenz](#) concentration and QTc prolongation was observed. Following administration of [efavirenz](#) 600 mg/day for 14 days, the mean C_{max} in subjects with the CYP2B6 *6/*6 genotype was 2.25-fold higher than the mean C_{max} in subjects with the CYP2B6 *1/*1 genotype and the mean QTc interval prolongation was 8.7 milliseconds in subjects with the CYP2B6 *6/*6 genotype [358].

3.5.1.EB] [Eletriptan](#)

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

2J) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[236], and [eletriptan](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment and at dosage increases is recommended if [eletriptan](#) and [amitriptyline](#) are used concurrently [978]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, and diarrhea), and mental status changes (eg, 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 [240].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [eletriptan](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. If coadministration is required, monitoring of the patient during treatment and at dosage increases is recommended [978].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.EC] Eliglustat

- 1J) Interaction Effect: increased eliglustat exposure and subsequent prolongation of the QT interval
- 2J) Summary: Coadministration of eliglustat, a CYP2D6 and CYP3A4 substrate, with strong or moderate CYP2D6 inhibitors, can result in increased eliglustat exposure and may cause serious [cardiac arrhythmias](#), including QT-interval prolongation. Coadministration with strong or moderate CYP2D6 inhibitors led to increases in eliglustat Cmax and AUC among extensive CYP2D6 metabolizers with [Gaucher disease type 1](#) and similar increases are expected to occur in intermediate CYP2D6 metabolizers. If coadministration in extensive or intermediate CYP2D6 metabolizers with [Gaucher disease type 1](#) is clinically indicated, reduce the eliglustat dose to 84 mg/day. Do not administer eliglustat with strong or moderate CYP2D6 inhibitors plus strong or moderate CYP3A4 inhibitors, as concurrent use is contraindicated for all patients[639].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Coadministration of eliglustat with strong or moderate CYP2D6 inhibitors may result in increased in eliglustat exposure that can progress to serious [cardiac arrhythmias](#), including QT-interval prolongation. If coadministration in extensive or intermediate metabolizers with [Gaucher disease type 1](#) is clinically indicated, reduce the eliglustat dose to 84 mg/day. Do not administer eliglustat with strong or moderate CYP2D6 inhibitors plus strong or moderate CYP3A4 inhibitors, as concurrent use is contraindicated for all patients[639].
- 7J) Probable Mechanism: inhibition of CYP2D6-mediated eliglustat metabolism
- 8J) Literature Reports

aJ) Coadministration of eliglustat 84 mg twice daily with the strong CYP2D6 inhibitor, [paroxetine](#) (30 mg/day), led to 7-fold and 8.4-fold increases in eliglustat Cmax and AUC, respectively, in extensive CYP2D6 metabolizers with [Gaucher disease type 1](#) (N=30). Intermediate CYP2D6 metabolizers were predicted to experience 2.1- and 2.3-fold increases in eliglustat Cmax and AUC, respectively. Among extensive CYP2D6 metabolizers treated eliglustat and [terbinafine](#), a moderate CYP2D6 inhibitor, simulations suggested that coadministration would cause eliglustat Cmax and AUC to rise 3.8-fold and 4.5-fold, respectively, and to increase 1.6-fold in intermediate CYP2D6 metabolizers [639]

bJ) Among extensive CYP2D6 metabolizers with [Gaucher disease type 1](#), simulations suggested that eliglustat Cmax and AUC would increase 16.7- and 24.2-fold, respectively, with concomitant use of [paroxetine](#) (a strong CYP2D6 inhibitor) plus [ketoconazole](#) (a strong CYP3A4 inhibitor). Among intermediate CYP2D6 metabolizers, the predicted eliglustat Cmax and AUC were 7.5- and 9.8-fold higher, respectively, with concurrent use of [paroxetine](#) plus [ketoconazole](#). Among extensive metabolizers, the predicted eliglustat Cmax and AUC were 16.7- and 24.2-fold higher, respectively, with concurrent use of [paroxetine](#) plus [ketoconazole](#). Treatment with moderate CYP2D6 and CYP3A inhibitors would increase eliglustat Cmax and AUC an estimated 10.2- and 13.6-fold, respectively, with concomitant use of [terbinafine](#) (a moderate CYP2D6 inhibitor) plus [fluconazole](#) (a moderate CYP3A inhibitor) among extensive CYP2D6 metabolizers, and would increase by 4.2- and 5-fold, respectively, among intermediate CYP2D6 metabolizers [639].

3.5.1.ED] Enflurane

- 1J) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)) and an increased risk of seizure activity
- 2J) Summary: [Enflurane](#) may prolong the QT interval in some patients[1008]. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent

administration of [enflurane](#) and tricyclic antidepressants is not recommended [1009]. Concomitant administration of [amitriptyline](#) and [enflurane anesthesia](#) has been reported to result in seizures in two cases [1010].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Avoid concurrent use of [enflurane](#) and tricyclic antidepressants, particularly in patients with a history of seizure activity or when hyperventilation or high concentrations of [enflurane](#) will be required.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Two case reports of patients on [amitriptyline](#) therapy who experienced seizure activity while receiving [enflurane anesthesia](#) have been documented [1007]. The first patient, a 42-year old female, was taking [amitriptyline](#) 100 mg daily. [Anesthesia](#) was induced with [fentanyl](#), [enflurane](#), and nitrous oxide. Approximately three hours after [anesthesia](#) was induced, clonic movements of the patient's right hand and forearm were noted. [Enflurane](#) concentration was 1% at the time. Changes in ventilation did not affect the involuntary movements, so [enflurane](#) was discontinued and replaced with [halothane](#) 1%. The movements decreased in frequency and amplitude and subsequently disappeared in approximately one minute. The second case report involved a 39-year old male who was taking [amitriptyline](#) 150 mg daily. [Anesthesia](#) was maintained with [enflurane](#) 1% to 2%, and intermittent clonic movements started in the right arm and leg approximately one hour into the surgery. [Enflurane](#) was discontinued and [halothane](#) was instituted, which caused the involuntary movements to disappear in approximately two minutes. No further movements were seen during the remaining three hours of [anesthesia](#).

3.5.1.EE] [Epinephrine](#)

1) Interaction Effect: [hypertension](#), [cardiac arrhythmias](#), and [tachycardia](#)

2) Summary: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [416] Clinical trials have demonstrated a 2- to 8-fold increase in the effects of [IV infusions](#) of alpha-adrenergic drugs to volunteers on tricyclic antidepressants. [Arrhythmias](#) and other severe adverse effects have also been reported [419][420][421][422].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [416]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of [norepinephrine](#) reuptake

8) Literature Reports

a) Four healthy volunteers received [IV infusions](#) of various sympathomimetic amines ([epinephrine](#), [norepinephrine](#), [phenylephrine](#), and [isoproterenol](#)) before and after [imipramine](#) (25 mg 3 times daily for 5 days). They showed an increased pressor response to [epinephrine](#) (2- to 4-fold), [norepinephrine](#) (4- to 8-fold), and [phenylephrine](#) (2- to 3-fold) after [imipramine](#), but no

difference was observed in the response to [isoproterenol](#). Thus, the increased pressor response appeared to occur only for alpha-adrenergic effects. All 4 subjects demonstrated changes in cardiac rhythm with [epinephrine](#) and [imipramine](#) consisting of sinus [arrhythmia](#) in 3 subjects and multiple [ectopic beats](#) and a [nodal rhythm](#) in the fourth subject [417].

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients who received a local anesthetic with [norepinephrine](#) (1:25,000) had severe reactions (severe headaches, chest tightness, [subarachnoid hemorrhage](#)). The drug history was incomplete, but at least 3 had been taking a tricyclic antidepressant at the time [418].

3.5.1.EF] [Erythromycin](#)

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

2) Summary: [Erythromycin](#) significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients [459]. [Erythromycin](#) has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval [460]. Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose [461]. Caution is advised with coadministration of drugs that potentially prolong the QTc interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if [erythromycin](#) and tricyclic antidepressants are used concomitantly. Monitor QT interval at baseline and periodically during treatment.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) [Erythromycin](#) did not significantly affect the metabolism of tricyclic antidepressants in a study of 8 patients. Patients were maintained on [desipramine](#) (n equal to 5), [imipramine](#) (n equal to 1), [doxepin](#) (n equal to 1), or [doxepin](#) (n equal to 1). All patients received [erythromycin](#) stearate 250 mg four times daily for six days while maintaining their usual tricyclic regimen. No change in the antidepressant or active metabolite concentrations was seen during coadministration with [erythromycin](#) [456].

b) Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose [457].

c) [Erythromycin](#) significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The [erythromycin](#) dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with [heart disease](#) (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without [heart disease](#) (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed [torsades de pointes](#) attributed to [erythromycin](#). Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater [458].

3.5.1.EG] [Escitalopram](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Escitalopram is a QT-interval-prolonging drug[394]. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Escitalopram is a QT-interval-prolonging drug[394]. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation.
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.EH] Eslicarbazepine Acetate

- 1) Interaction Effect: increased exposure of CYP2C19 substrates
- 2) Summary: Concurrent administration of eslicarbazepine acetate (a CYP2C19 inhibitor) with a CYP2C19 substrate may increase the exposure of the CYP2C19 substrate[508]. If coadministering, use caution and monitor the patient closely.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of eslicarbazepine acetate (a CYP2C19 inhibitor) with a CYP2C19 substrate may increase the exposure of the CYP2C19 substrate[508]. If coadministering, use caution and monitor the patient closely.
- 7) Probable Mechanism: inhibition of CYP2C19-mediated metabolism by eslicarbazepine acetate

3.5.1.EI] Esterified Estrogens

- 1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[997], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [998]. The effects of the interaction appear to be estrogen dose-related [999] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [1000].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: established
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
- 8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 mg daily) and placebo, five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (50 mcg daily), while five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after two weeks, the five patients that received

[imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received [imipramine](#) 150 mg and [ethinyl estradiol](#) 50 mcg daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [988].

b) A 32-year-old female taking [conjugated estrogens](#) 2.5 mg and [imipramine](#) 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [989] [990].

c) In a study women received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [991].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 mg at bedtime while 19 took [clomipramine](#) 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [992].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 mg daily for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 mg daily for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 mg was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogen](#) 1.25 mg daily who was prescribed [amitriptyline](#) 50 mg daily for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogen](#) 1.25 mg daily and [amitriptyline](#) 50 mg daily. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [993].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 mcg or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [994].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [995]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [996].

3.5.1.EJ] Estradiol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[997], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [998]. The effects of the interaction appear to be estrogen dose-related [999] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [1000].

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 mg daily) and placebo, five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (50 mcg daily), while five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after two weeks, the five patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received [imipramine](#) 150 mg and [ethinyl estradiol](#) 50 mcg daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [988].

b) A 32-year-old female taking [conjugated estrogens](#) 2.5 mg and [imipramine](#) 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [989] [990].

c) In a study women received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [991].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 mg at bedtime while 19 took [clomipramine](#) 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [992].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 mg daily for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 mg daily for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 mg was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogen](#) 1.25 mg daily who was prescribed [amitriptyline](#) 50 mg daily for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogen](#) 1.25 mg daily and [amitriptyline](#) 50 mg daily. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [993].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 mcg or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [994].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [995]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [996].

3.5.1.EK] [Estradiol](#) Cypionate

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.EL] [Estradiol Valerate](#)

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of

the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b)) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c)) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d)) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e)) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after

taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.EM] Estriol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[997], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [998]. The effects of the interaction appear to be estrogen dose-related [999] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [1000].

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 mg daily) and placebo, five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (50 mcg daily), while five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after two weeks, the five patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received [imipramine](#) 150 mg and [ethinyl estradiol](#) 50 mcg daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [988].

b) A 32-year-old female taking [conjugated estrogens](#) 2.5 mg and [imipramine](#) 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant

headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [989] [990].

c) In a study women received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [991].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 mg at bedtime while 19 took [clomipramine](#) 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [992].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 mg daily for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 mg daily for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 mg was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogen](#) 1.25 mg daily who was prescribed [amitriptyline](#) 50 mg daily for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogen](#) 1.25 mg daily and [amitriptyline](#) 50 mg daily. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [993].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 mcg or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [994].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [995]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [996].

3.5.1.EN] [Estrone](#)

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[997], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [998]. The effects of the interaction appear to be estrogen dose-related [999]

and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [1000].

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: established

6J) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7J) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8J) Literature Reports

aJ) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 mg daily) and placebo, five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (50 mcg daily), while five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after two weeks, the five patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received [imipramine](#) 150 mg and [ethinyl estradiol](#) 50 mcg daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [988].

bJ) A 32-year-old female taking [conjugated estrogens](#) 2.5 mg and [imipramine](#) 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [989] [990].

cJ) In a study women received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [991].

dJ) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 mg at bedtime while 19 took [clomipramine](#) 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#)

concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [992].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 mg daily for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 mg daily for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 mg was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogen](#) 1.25 mg daily who was prescribed [amitriptyline](#) 50 mg daily for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogen](#) 1.25 mg daily and [amitriptyline](#) 50 mg daily. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [993].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 mcg or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [994].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [995]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [996].

3.5.1.EO| [Estropipate](#)

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[997], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [998]. The effects of the interaction appear to be estrogen dose-related [999] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [1000].

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 mg daily) and placebo, five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (50 mcg daily), while five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the

10 patients taking [imipramine](#) alone. However, after two weeks, the five patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received [imipramine](#) 150 mg and [ethinyl estradiol](#) 50 mrg daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [988].

b)) A 32-year-old female taking [conjugated estrogens](#) 2.5 mg and [imipramine](#) 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [989] [990].

c)) In a study women received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [991].

d)) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 mg at bedtime while 19 took [clomipramine](#) 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [992].

e)) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 mg daily for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 mg daily for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 mg was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogen](#) 1.25 mg daily who was prescribed [amitriptyline](#) 50 mg daily for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogen](#) 1.25 mg daily and [amitriptyline](#) 50 mg daily. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [993].

f)) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 mcg or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [994].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [995]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [996].

3.5.1.EP] Eterobarb

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.EQ] [Ethchlorvynol](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[220].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

3.5.1.ER] [Ethinyl Estradiol](#)

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes
- 8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the

groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.ES| [Ethynodiol Diacetate](#)

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

- 7j) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes
- 8j) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2

milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.ET] Etilefrine

1) Interaction Effect: [hypertension](#), [cardiac arrhythmias](#), and [tachycardia](#)

2) Summary: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [416] Clinical trials have demonstrated a 2- to 8-fold increase in the effects of [IV infusions](#) of alpha-adrenergic drugs to volunteers on tricyclic antidepressants. [Arrhythmias](#) and other severe adverse effects have also been reported [419][420][421][422].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [416]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of [norepinephrine](#) reuptake

8) Literature Reports

a) Four healthy volunteers received [IV infusions](#) of various sympathomimetic amines ([epinephrine](#), [norepinephrine](#), [phenylephrine](#), and [isoproterenol](#)) before and after [imipramine](#) (25 mg 3 times daily for 5 days). They showed an increased pressor response to [epinephrine](#) (2- to 4-fold), [norepinephrine](#) (4- to 8-fold), and [phenylephrine](#) (2- to 3-fold) after [imipramine](#), but no difference was observed in the response to [isoproterenol](#). Thus, the increased pressor response appeared to occur only for alpha-adrenergic effects. All 4 subjects demonstrated changes in cardiac rhythm with [epinephrine](#) and [imipramine](#) consisting of sinus [arrhythmia](#) in 3 subjects and multiple [ectopic beats](#) and a [nodal rhythm](#) in the fourth subject [417].

b)) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients who received a local anesthetic with [norepinephrine](#) (1:25,000) had severe reactions (severe headaches, chest tightness, [subarachnoid hemorrhage](#)). The drug history was incomplete, but at least 3 had been taking a tricyclic antidepressant at the time [418].

3.5.1.EU] [Etodolac](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: unknown

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.EV] [Etofenamate](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: unknown

8)) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.EW] Etonogestrel

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12

subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.EX] Etoricoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding.

including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.EY] Felbinac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.EZ] Fenoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.FA] [Fentanyl](#)

1) Interaction Effect: increased risk of CNS depression

2) Summary: Coadministration of [fentanyl](#), a CNS depressant, with other CNS depressants may cause additive CNS depression including [respiratory depression](#), hypotension, and profound sedation, which could potentially lead to coma or death[201]. Severe hypotension has been reported with coadministration of [fentanyl](#) and [midazolam](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [202]. Due to the risk of additive CNS effects, use caution, monitor patients closely, and reduce the dose of one or both when these agents are administered concomitantly [201].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [fentanyl](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Due to the added CNS depressant effects, exercise caution if coadministration of [fentanyl](#) and another CNS depressant is required. Carefully monitor patients receiving concomitant [fentanyl](#) and other CNS depressants and adjust dosage of one or both agents[201].

7) Probable Mechanism: additive CNS depression

3.5.1.FB] [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[529], including SSRIs [531][530][532]. [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 [529]. 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 [240].

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](#)) [529]. 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 [240].

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 [cyproheptadine](#). After 3 days, the patient's temperature and CPK level normalized and she later extubated with no further complications [530].

b) [Serotonin syndrome](#) following the administration of IV [fentanyl](#) during surgical procedures was reported in 2 patients also taking SSRIs ([sertraline](#) and escitalopram). The first patient received IV [fentanyl](#) (50 micrograms), [midazolam](#) (2 mg), and 2 doses [propofol](#) (60 mg and 40 mg) in an [outpatient surgery](#) center prior to a [carpal tunnel release](#) procedure. Postoperatively the patient began shivering and became increasingly agitated for which she was transferred to the emergency department. On presentation the patient was combative, diaphoretic, confused, was unable to follow commands, tachycardic, hypertensive, had hyperreflexia, and ankle clonus. Baseline [creatinine kinase](#) rose to 613 units/L on day 2 of hospitalization. The toxicology service treated her with escalating doses of benzodiazepines with no improvement. The patient was subsequently intubated and sedated with a continuous [propofol](#) infusion. After 2 days the patient was extubated and by day 3 all symptoms had resolved and the patient was discharged home. The second patient was a 59-year-old woman admitted for an [omentectomy](#) for which she received IV [fentanyl](#) 250 micrograms, [etomidate](#), vecuronium, [morphine](#) and cephazolin. Following [extubation](#) the patient became hypoxic and acidotic and was reintubated and transferred to the ICU. On postoperative day 1 she was extubated and later became tachycardic and was unable to follow commands. On examination the patient was agitated and diaphoretic, had patellar hyperreflexia and a bilateral 3 to 4 beat ankle clonus. Laboratory evaluation was remarkable for a peak [creatinine kinase](#) of 1161 units/L on postoperative day 2. The patient was treated with [lorazepam](#) and [cyproheptadine](#) with resolution of symptoms after 3 days [531].

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 [532].

3.5.1.FC] Fepradinol

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.FD] Feprazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.FE] Fingolimod

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Both [amitriptyline](#) and fingolimod may prolong the QT interval and concomitant use should be approached with caution[392][236]. Initiating fingolimod therapy may decrease heart rate and prolong the QT interval. Drugs that prolong the QT interval, such as [amitriptyline](#), may increase the risk of [torsade de pointes](#) in patients with bradycardia [392]. Monitoring for QT interval prolongation may be warranted if these agents are used concurrently.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and fingolimod as this may result in additive effects on the QT interval, and may increase the risk of serious cardiovascular effects including [torsade de pointes](#)[392]. If coadministration is required, QT interval monitoring may be warranted.

7) Probable Mechanism: additive QT interval prolongation

3.5.1.FF] [Flecainide](#)

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

2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended[467][468][469].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [465].

b) A 68-year-old man suffering from agitated [major depression](#) was begun on a dose of [desipramine](#) 125 mg daily which produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An increased dose of 175 mg daily produced excellent clinical response with no side effects. He developed [atrial fibrillation and flutter](#). [Digoxin](#) 0.25 mg daily was added to his therapy, and [desipramine](#) was discontinued. His [arrhythmia](#) was suppressed with the

addition of [propafenone](#) 150 mg twice daily and 300 mg at bedtime. [Desipramine](#) 150 mg daily was again begun, at which point he experienced dry mouth, sedation, and shakiness; the [desipramine](#) serum level was measured at 2092 nmol/L. The [desipramine](#) was discontinued for five days, the side effects ceased, and [desipramine](#) therapy was resumed at 75 mg daily. The [desipramine](#) serum level was measured at 1130 nmol/L [466].

3.5.1.FG] Flibanserin

- 1) Interaction Effect: additive CNS depression
- 2) Summary: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[173].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[173].
- 7) Probable Mechanism: additive CNS depression

3.5.1.FH] Floctafenine

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.FI] Fluconazole

- 1) Interaction Effect: an increased risk of [amitriptyline](#) toxicity and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Coadministration of [fluconazole](#) and [amitriptyline](#) may increase [amitriptyline](#) effects[242]. Several case reports have described increased [amitriptyline](#) concentrations and signs of toxicity, including QT prolongation and [torsades de pointes](#), when [amitriptyline](#) was used in combination with [fluconazole](#)

[243][244][245]. If concomitant use is required, measure S-amitriptyline levels prior to initiation of concomitant use and repeat measurement 1 week later. Adjust [amitriptyline](#) dosage if necessary [242]. Consider monitoring patients with pre-existing [cardiovascular disorders](#) who require concomitant therapy. .

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [fluconazole](#) as concomitant use may cause increased [amitriptyline](#) effects[242] and an increased risk for cardiotoxic reactions, including QT prolongation and [torsades de pointes](#)[243][244][245]. If concomitant use is required, consider measuring S-amitriptyline levels prior to initiation of concomitant use and repeat measurement 1 week later. Adjust [amitriptyline](#) dosage if necessary [242]. Consider monitoring patients with pre-existing [cardiovascular disorders](#) who require concomitant therapy.

7) Probable Mechanism: additive prolongation of cardiac conduction time

8) Literature Reports

a) Three case reports describe increased [amitriptyline](#) levels with [fluconazole](#). Patient 1, a 39-year-old male, was taking [fluconazole](#) 200 mg daily and [amitriptyline](#) 25 mg three times daily. Three days after [amitriptyline](#) was increased to 50 mg three times daily to treat neuropathic pain, the patient experienced visual hallucinations and had a serum [amitriptyline](#) level of 724 ng/mL (therapeutic level, 150 ng/mL to 250 ng/mL). Patient 2, a 35-year-old male, was taking [amitriptyline](#) 50 mg per day. After [fluconazole](#) 100 mg daily was added following a loading dose of 200 mg, the patient had a serum [amitriptyline](#) level of 349 ng/mL on day 33 of combined therapy. The patient did not experience any behavioral changes. Patient 3, a 43-year-old male with [end-stage renal disease](#), had received [amitriptyline](#) 100 mg per day for over a year. After receiving [fluconazole](#) doses of 200 mg to 400 mg daily for five days after a loading dose of 1000 mg, the patient's serum [amitriptyline](#) level was 1224 ng/mL. The patient experienced [cardiac arrest](#) eight days later and died after a complicated hospital course. In all of the cases, patients were on several other continuous medications. The authors suggest that the addition of [fluconazole](#) caused increases in serum [amitriptyline](#), possibly due to fluconazole-induced inhibition of cytochrome P450 isozymes [246].

b) A 57-year-old female presented to an emergency department with complaints of several episodes of loss of consciousness, all occurring while the patient was seated. Chest pressure was present after each episode. Medications included [amitriptyline](#) for the previous five weeks, [sertraline](#) 100 mg daily for the previous seven months, [fluconazole](#), [lisinopril](#), and an iron supplement. An [electrocardiogram](#) (ECG) three months prior to presentation showed a normal sinus rhythm with a normal QT interval. Upon hospital admission, the patient had several episodes of [torsades de pointes](#) recorded in leads II and VI that were accompanied by near syncope while the patient was supine. [Amitriptyline](#) was discontinued and [fluconazole](#) was reduced to 200 mg daily. Follow-up ECGs showed progressive normalization of the QT interval and ECGs three and six months after hospitalization were normal [247].

c) A 12-year-old boy with prostatic [rhabdomyosarcoma](#) experienced temporary loss of consciousness associated with concomitant [fluconazole](#) and [amitriptyline](#) treatment. The syncopal episodes occurred periodically over approximately seven months, and coincided with the addition of [fluconazole](#) to his drug regimen which included [amitriptyline](#). The patient previously tolerated each medication when given exclusively. The patient experienced no further episodes of syncope after [amitriptyline](#) was discontinued [248].

3.5.1.FJ] Flufenamic Acid

- 1J) Interaction Effect: an increased risk of bleeding
- 2J) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: established
- 6J) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7J) Probable Mechanism: unknown
- 8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.FK] Flumazenil

- 1J) Interaction Effect: precipitation of seizures
- 2J) Summary: Concomitant use of [flumazenil](#) and benzodiazepines is contraindicated in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Abrupt discontinuation of the protective effect of a benzodiazepine agonist can cause seizures in epileptic patients[118].
- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of [flumazenil](#) and benzodiazepines is contraindicated in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Abrupt discontinuation of the protective effect of a benzodiazepine agonist can cause seizures in epileptic patients[118].
- 7J) Probable Mechanism: abrupt discontinuation of the anticonvulsant protective effect

3.5.1.FL] Fluoxetine

- 1J) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)
- 2J) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[509]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [510][516][517][518][519][520]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently

discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [509].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[509]

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

8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [509].

b) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [510].

c) Concomitant administration of [fluoxetine](#) and [desipramine](#) was reported to result in an increased [desipramine](#) level and new onset of [delirium](#) in a 69-year-old male within 10 days of the addition of [fluoxetine](#) to the patient's regimen [511].

d) [Fluoxetine](#) increased the level of tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) in 4 patients. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [512].

e) A 39-year-old female experienced symptomatic increases in her [desipramine](#) levels with concomitant [fluoxetine](#) therapy. Prior to [fluoxetine](#) therapy, the patient's measured levels of [desipramine](#) had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of [fluoxetine](#) 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a [desipramine](#) level of 527 ng/mL (1978 nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#) dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [513].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [514].

g) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [515].

3.5.1.FM] [Flurbiprofen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.FN] [Fluvoxamine](#)

1) Interaction Effect: [amitriptyline](#) toxicity (dry mouth, urinary retention, sedation)

2) Summary: Coadministration of [fluvoxamine](#) and [amitriptyline](#) was found to significantly increase plasma levels of [amitriptyline](#)[843]. A bidirectional effect was suggested in which [fluvoxamine](#) increased [amitriptyline](#) concentrations (by interfering with N-demethylation) and [amitriptyline](#) increased [fluvoxamine](#) levels [844].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

- 6) Clinical Management: Monitor patients for signs of [amitriptyline](#) and [fluvoxamine](#) toxicity; lower doses of one or both agents may be required with concomitant therapy.
- 7) Probable Mechanism: decreased [amitriptyline](#) metabolism
- 8) Literature Reports

a) [Fluvoxamine](#) has been shown to significantly increase plasma levels of [amitriptyline](#) and [clomipramine](#) and to mildly increase levels of their metabolites [nortriptyline](#) and desmethyldomipramine, respectively. This may be due to competitive inhibition of oxidative metabolism in the liver [841].

b) Metabolism of tricyclic antidepressants coadministered with [fluvoxamine](#) was studied in eight depressed patients (one patient received [amitriptyline](#)) [842]. [Fluvoxamine](#) was found to interfere with N-demethylation of [amitriptyline](#). The combination of [fluvoxamine](#) and [amitriptyline](#) led to increased plasma levels of [amitriptyline](#) and decreased concentrations of [amitriptyline's](#) N-demethylated metabolite, [nortriptyline](#). In addition, plasma levels of [fluvoxamine](#) were increased.

3.5.1.FO] [Formoterol](#)

- 1) Interaction Effect: an increased risk of cardiovascular excitation
- 2) Summary: Concurrent administration of [formoterol](#) with a tricyclic antidepressant (TCA) may lead to potentiation of [formoterol's](#) adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if [formoterol](#) is administered to patients who are being treated with a TCA[921]. Monitor patients closely for adverse cardiovascular effects.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Extreme caution and close observation for adverse cardiovascular effects are warranted when [formoterol](#) is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects of [formoterol](#) can be potentiated by TCAs[921].
- 7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.FP] [Fosamprenavir](#)

- 1) Interaction Effect: increased tricyclic agent serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: Coadministration of [fosamprenavir](#) with a tricyclic antidepressant may provoke increased serum concentrations of the tricyclic antidepressant, causing a potential risk of [arrhythmias](#) or other serious adverse effects. [Fosamprenavir](#) is a prodrug of [amprenavir](#), an inhibitor of the CYP3A4 isoenzyme in addition to being a CYP3A4 substrate. Tricyclic agents may partially depend on the CYP3A4 pathway for metabolism. Plasma concentrations of the tricyclic agent should be closely monitored in patients also receiving [fosamprenavir](#)[412].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: If concomitant therapy with [fosamprenavir](#) and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic agent should be closely monitored. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))[412].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated tricyclic agent metabolism

3.5.1.FQ| Foscarnet

- 1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsades de pointes**, **cardiac arrest**)
- 2) Summary: **Foscarnet** can prolong the QT interval in some patients, which may result in **ventricular tachycardia**, **ventricular fibrillation**, and **torsades de pointes**. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of **arrhythmias**, the concurrent administration of **foscarnet** and tricyclic antidepressants is not recommended[1003][1004].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of **foscarnet** and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive cardiac effects

3.5.1.FR| Fosphenytoin

- 1) Interaction Effect: alterations in serum **phenytoin** concentrations
- 2) Summary: Concurrent **phenytoin** use with some benzodiazepines occasionally has led to either increased or decreased serum levels of **phenytoin**, as well as lowered levels of the benzodiazepine, particularly **clonazepam**[222][223][224][225].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients for continuing clinical signs of **phenytoin** effectiveness and/or emergence of **phenytoin** toxicity. Routine serum **phenytoin** serum concentrations should be obtained one week after the addition or withdrawal of benzodiazepine therapy.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) There have been reports of clinical intoxication associated with high **phenytoin** serum levels in patients receiving nitrazepam in combination with **phenytoin** [221].

3.5.1.FS| Fosphenytoin

- 1) Interaction Effect: an increased risk of **phenytoin** toxicity (ataxia, hyperreflexia, **nystagmus**, tremor)
- 2) Summary: A few case reports have indicated that **imipramine** inhibits **phenytoin** metabolism resulting in increased serum **phenytoin** concentration[573][574]. Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because **phenytoin** is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor therapeutic efficacy of **amitriptyline**; an increased dose may be required. Serum **phenytoin** levels should be obtained when tricyclic antidepressant agents are added to therapy due to the potential for impaired **phenytoin** metabolism.
- 7) Probable Mechanism: inhibition of **phenytoin** metabolism

3.5.1.FT| Fospropofol

- 1) Interaction Effect: additive cardiorespiratory effects
- 2) Summary: Concomitant use of fospropofol and a benzodiazepine may result in additive cardiorespiratory effects due to the sedative action of both drugs[100]. Monitoring the patient for adverse effects may be warranted and possible dose adjustments may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when fospropofol and a benzodiazepine are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.FU] Frovatriptan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported in patients who have used [frovatriptan](#) concomitantly with a tricyclic antidepressant. Symptoms of [serotonin syndrome](#) generally occur within minutes to hours after addition or dose increase of a serotonergic agent.[241]. Concomitant use should be approached with caution due to additive serotonergic effects and the increased risk of [serotonin syndrome](#). 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 [240]. Therefore, if [serotonin syndrome](#) is suspected, discontinue use of [frovatriptan](#) [241]. Alternatively, if [serotonin syndrome](#) develops, discontinue both offending agents ([frovatriptan](#) and the tricyclic antidepressant) and provide supportive care and other therapy as necessary [240].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [frovatriptan](#) and a tricyclic antidepressant[240], as it may result in [serotonin syndrome](#), which may be life-threatening. Symptoms of [serotonin syndrome](#) generally occur within minutes to hours after addition or dose increase of a serotonergic agent. If these agents are coadministered and [serotonin syndrome](#) is suspected, discontinue use of [frovatriptan](#) [241]. Alternatively, if [serotonin syndrome](#) develops, discontinue both offending agents ([frovatriptan](#) and the tricyclic antidepressant) and provide supportive care and other therapy as necessary [240].
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.FV] Furazolidone

- 1) Interaction Effect: [neurotoxicity](#), seizures, or [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: There is a single case report of toxic [psychosis](#) occurring shortly after the initiation of [furazolidone](#) therapy in a patient taking [amitriptyline](#) and other medications[521]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [522].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: probable

6) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.

7) Probable Mechanism: altered catecholamine uptake and metabolism

3.5.1.FW] [Galantamine](#)

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

2) Summary: Based upon in vitro studies, the major enzymes involved in [galantamine](#) metabolism are CYP3A4 and CYP2D6. [Amitriptyline](#) is a known inhibitor of CYP2D6. In a population pharmacokinetic analysis using a database of 852 [Alzheimer's disease](#) patients, several drugs which inhibit CYP2D6, including [amitriptyline](#) (N=17), demonstrated a 25-33% decrease in [galantamine](#) clearance. The resulting plasma concentration increase of [galantamine](#) may warrant caution when it is coadministered with [amitriptyline](#). Monitor for [galantamine](#) toxicity including anorexia, nausea, vomiting, dizziness, [arrhythmias](#) or [gastrointestinal bleeding](#)[610].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Increased [galantamine](#) plasma concentrations may result from [amitriptyline](#) inhibition of [galantamine](#) CYP2D6-mediated metabolism. Monitor for [galantamine](#) toxicity including anorexia, nausea, vomiting, dizziness, [arrhythmias](#), or [gastrointestinal bleeding](#)[610].

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

3.5.1.FX] [Gatifloxacin](#)

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

2) Summary: [Gatifloxacin](#) may prolong the QT interval in some patients, which may result in [ventricular tachycardia](#), [ventricular fibrillation](#), and [torsades de pointes](#). Although [pharmacokinetic studies](#) between [gatifloxacin](#) and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of [gatifloxacin](#) and a tricyclic antidepressant is not recommended[976].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of [gatifloxacin](#) and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FY] [Gemifloxacin](#)

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

2) Summary: Although [pharmacokinetic studies](#) between gemifloxacin and drugs that prolong the QT interval, such as tricyclic antidepressants, have not been performed, gemifloxacin should be used cautiously when given concurrently with tricyclic antidepressants[975].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

- 6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as gemifloxacin and tricyclic antidepressants, is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FZ] [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[984][985][986]. 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[984][985][986].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.GA] [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[984][985][986]. 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[984][985][986].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.GB] [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](#)[784] and the risk of QT-interval prolongation [785]. [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 [784]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [785].
- 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](#)[784] and the risk of QT-interval prolongation [785]. 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 [784]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [785].

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

3.5.1.GC] [Grepafloxacin](#)

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

2) Summary: Healthy volunteers who received [grepafloxacin](#) during a Phase I study experienced prolongation of the QTc interval. On an outpatient basis, [grepafloxacin](#) is contraindicated with other drugs that are known to also prolong the QTc interval or cause [torsades de pointes](#), including tricyclic antidepressants. When appropriate cardiac monitoring can be assured, such as in the hospitalized patient, these two agents should be coadministered with caution[895].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The concurrent use of [grepafloxacin](#) and tricyclic antidepressants is contraindicated unless appropriate cardiac monitoring can be assured, such as in the hospitalized patient.

7) Probable Mechanism: additive cardiac effects

3.5.1.GD] [Guanadrel](#)

1) Interaction Effect: decreased antihypertensive effectiveness

2) Summary: Tricyclic antidepressants inhibit the uptake of [guanethidine](#), and possibly [guanadrel](#), into the adrenergic neuron, resulting in an inhibition of its antihypertensive effect[934][935]. When a patient is on concomitant tricyclic antidepressant and [guanadrel](#) therapy, caution should be exercised when the tricyclic antidepressant is discontinued, since an exaggerated effect of [guanadrel](#) may be seen [936].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher doses of [guanadrel](#) may be required. An alternative class of antihypertensive agent, such as an angiotensin-converting enzyme inhibitor might be considered.

7) Probable Mechanism: decreased uptake of [guanadrel](#) into adrenergic neurons

3.5.1.GE] [Guanethidine](#)

1) Interaction Effect: decreased antihypertensive effectiveness

2) Summary: Tricyclic antidepressants inhibit the uptake of [guanethidine](#), and possibly [guanadrel](#), into the adrenergic neuron, resulting in an inhibition of the antihypertensive effect[634][635][636][637][638].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher doses of [guanethidine](#) may be required. An alternative class of antihypertensive agent, such as an angiotensin-converting enzyme inhibitor, might be considered.

7) Probable Mechanism: decreased uptake of [guanethidine](#) into adrenergic neurons

3.5.1.GF] Guanfacine

- 1) Interaction Effect: decreased antihypertensive effectiveness
- 2) Summary: Concomitant [clonidine](#) and tricyclic antidepressant therapy may impair the antihypertensive effects of [clonidine](#). Since the mechanism of action of [guanfacine](#) is similar to [clonidine](#), patients stabilized on [guanfacine](#) should be monitored for a hypertensive response when [amitriptyline](#) therapy is started[965][966].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher doses of [guanfacine](#) may be required. An alternative class of antihypertensive agent, such as an angiotensin-converting enzyme inhibitor might be considered.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A case of a hypertensive female who was maintained on [guanfacine](#) 2 mg daily with mean blood pressure at 138/89 mm Hg was reported [964]. After [amitriptyline](#) 75 mg daily was begun, her mean blood pressure was 150/100 mm Hg; upon discontinuation of the [amitriptyline](#), the blood pressure returned to 136/91 mm Hg. A month later she was given [imipramine](#) 50 mg daily and experienced similar changes in loss of blood pressure control; upon discontinuation of [imipramine](#), the blood pressure again returned to 137/90 mm Hg.

3.5.1.GG] Halofantrine

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Halofantrine](#) can prolong the QT interval in some patients, which may result in [ventricular tachycardia](#), [ventricular fibrillation](#), and [torsades de pointes](#). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [halofantrine](#) and tricyclic antidepressants is not recommended[620][621].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: The concurrent administration of [halofantrine](#) and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive cardiac effects

3.5.1.GH] Haloperidol

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Several antipsychotic agents are associated with QT-interval prolongation[282][283][284][285][286]. Although no formal drug interaction studies have been done, coadministration of a tricyclic antidepressant with an antipsychotic is not recommended [287].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7J) Probable Mechanism: additive cardiac effects

8J) Literature Reports

aJ) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [281].

3.5.1.GI] [Halothane](#)

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

2J) Summary: [Halothane](#) may prolong the QT interval in some patients[859]. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [halothane](#) and tricyclic antidepressants is not recommended [860].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of [halothane](#) and tricyclic antidepressants is not recommended.

7J) Probable Mechanism: additive effects on QT prolongation

3.5.1.GJ] [Heptabarbital](#)

1J) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2J) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7J) Probable Mechanism: increased tricyclic antidepressant metabolism

8J) Literature Reports

aJ) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism

of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.GK] Hexobarbital

- 1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
- 2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
- 7) Probable Mechanism: increased tricyclic antidepressant metabolism
- 8) Literature Reports

a) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.GL] [Histrelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[984][985][986]. 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[984][985][986].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.GM] [Hydrocodone](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: Use caution with the concomitant use of [hydrocodone](#) and a CNS depressant as this may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and consider using a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[226]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [hydrocodone](#) and a CNS depressant may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and use a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[226]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression

3.5.1.GN] Hydromorphone

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.GO] Hydroxychloroquine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: [Hydroxychloroquine](#) has been associated with QT interval prolongation[949][950], [ventricular premature contractions](#), and [torsade de pointes](#) [950]. 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[949] [950]. 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 [949].

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 [950].

3.5.1.GP| Hydroxytryptophan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2) Summary: Very rare cases of [serotonin syndrome](#) have been associated with the concomitant use of [amitriptyline](#) with other serotonergic agents[236], such as hydroxytryptophan. Concomitant use should be approached with caution due to the risk of additive effects and the potential for [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [amitriptyline](#) and hydroxytryptophan are used concurrently.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and hydroxytryptophan, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.GQ| 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[980]. 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[980]. 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.GR| [Ibuprofen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.GS| [Ibutilide](#)

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

2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[330], [amiodarone](#) [331], azimilide [332], [bretylum](#) [333], [ibutilide](#) [334], sotalol [335], [dofetilide](#) [336], and [sotalol](#) [337]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [338][339].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7J) Probable Mechanism: additive QT prolongation

8J) Literature Reports

aJ) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [328].

bJ) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised [329].

3.5.1.GTJ Iloperidone

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

2J) Summary: Avoid using [amitriptyline](#) and iloperidone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[294].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid using [amitriptyline](#) and iloperidone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[294].

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

3.5.1.GUJ Imipramine

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

2J) Summary: Concomitant use of [amitriptyline](#) and [imipramine](#) is not common clinical practice. However if using [amitriptyline](#) and [imipramine](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236]. Both [amitriptyline](#), a serotonin reuptake inhibitor [236], and [imipramine](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [imipramine](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, and diarrhea), and mental status changes (eg, 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 [240].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [amitriptyline](#) and [imipramine](#) is not common clinical practice. However if using [amitriptyline](#) and [imipramine](#) concomitantly, use caution due to a potential for additive effects on the QT interval and an increased risk of serious cardiovascular effects and/or additive serotonergic effects and an increased risk of [serotonin syndrome](#)[236].

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

3.5.1.GVJ Indomethacin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.GW] [Iobenguane I 123](#)

- 1) Interaction Effect: potential for false negative imaging results
- 2) Summary: Iobenguane is similar in structure to the neurotransmitter [norepinephrine](#) and is taken up by the [norepinephrine](#) transporter in adrenergic nerve terminals. It is stored in the presynaptic storage vesicles. Iobenguane will accumulate in adrenergically innervated tissues and labeling iobenguane with the isotope [iodine 123](#) will provide images of specific organs and tissues. Antidepressants that inhibit [norepinephrine](#) transporter function, such as SSRIs, tricyclic antidepressants, and MAOIs, may interfere with the clinical efficacy of [iobenguane I 123](#). Increasing the dose of [iobenguane I 123](#) will not overcome any potential [norepinephrine](#) uptake inhibition by these drugs. If [iobenguane I 123](#) imaging is necessary, discontinue this drug for at least 5 biological half-lives when clinically feasible[861].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [iobenguane I 123](#) and this drug has the potential to inhibit [norepinephrine](#) transporter function and cause false negative imaging results. Increasing the dose of [iobenguane I 123](#) will not overcome any potential [norepinephrine](#) uptake inhibition by these drugs. If [iobenguane I 123](#) imaging is necessary, discontinue this drug for at least 5 biological half-lives when clinically feasible[861].
- 7) Probable Mechanism: inhibition of [norepinephrine](#) transporter function by antidepressants

3.5.1.GX] [Iproniazid](#)

- 1) Interaction Effect: [neurotoxicity](#), seizures, or [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[714][715][716][717]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic

hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [718]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [719].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [696][697][698][699][700][701]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [702].

b) The development of [serotonin syndrome](#) due to administration of a TCA after MAOI therapy has been reported. In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [703].

c) A 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [704].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [705].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [706].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranylcypromine](#) in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to [disseminated intravascular coagulation](#) and eventual death [707].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranylcypromine](#) in any combination, and d) close monitoring of patients [708] [698][699][709][710]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [711]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [711]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [712][699][713].

3.5.1.GY] [Isocarboxazid](#)

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

2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[880][881][882][883]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [884]. The concurrent administration of [amitriptyline](#) and a MAOI, including [isocarboxazid](#), is contraindicated [885][886].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOI) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [862][863][864][865][866][867]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [868].

b) The development of [serotonin syndrome](#) was reported due to administration of a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent

[clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [869].

c) A drug interaction was reported when a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [870].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [871].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [872].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranylcypromine](#) in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexial state led to [disseminated intravascular coagulation](#) and eventual death [873].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranylcypromine](#) in any combination, and d) close monitoring of patients [874] [864][865][875][876]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [877]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added [591]. Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [877]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [878][865][879].

3.5.1.GZ| [Isoflurane](#)

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

2)) Summary: [Isoflurane](#) may prolong the QT interval in some patients[556]. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [isoflurane](#) and tricyclic antidepressants is not recommended [557].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of [isoflurane](#) and a tricyclic antidepressant is not recommended.

7)) Probable Mechanism: additive effect on QT prolongation

3.5.1.HA| [Isradipine](#)

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

2)) Summary: [Isradipine](#) can prolong the QT interval in some patients, which may result in [ventricular tachycardia](#), [ventricular fibrillation](#), and [torsades de pointes](#). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [isradipine](#) with a tricyclic antidepressant is not recommended[539][540].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concurrent administration of [isradipine](#) and a tricyclic antidepressant is not recommended.

7)) Probable Mechanism: additive cardiac effects

3.5.1.HB| [Ivabradine](#)

1)) Interaction Effect: increased risk of QT prolongation

2)) Summary: Use caution with the concomitant administration of ivabradine and other drugs that prolong the QT interval due to the potential for additive QT prolongation[960].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution with the concomitant administration of ivabradine and other drugs that prolong the QT interval due to the potential for additive QT prolongation[960].

7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.HC| [Kava](#)

1)) Interaction Effect: increased central nervous system depression

2)) Summary: Concomitant use of kava and a benzodiazepine may result in enhanced central nervous system depression. A case report describes a patient experiencing a semicomatose state likely due to concomitant use of kava and [alprazolam](#)[175]. In vitro data suggests this is most likely attributed to an increase in [GABA](#) binding sites in selected areas of the brain [176].

3)) Severity: moderate

4)) Onset: delayed

5)) Substantiation: theoretical

6)) Clinical Management: Avoid concomitant use of kava and benzodiazepines. For patients who choose to use the combination despite this advice, monitor closely for sedation, drowsiness, slowed reflexes, and other indicators of central nervous system depression. Advise against activities that require mental and psychomotor acuity (e.g., handling of heavy machinery).

7J) Probable Mechanism: additive effects on GABA receptor binding

8J) Literature Reports

aJ) A 54-year-old man was hospitalized in a lethargic and disoriented state attributed to concomitant administration of kava with alprazolam for 3 days. The doses of neither medication were provided. The patient was also taking cimetidine and terazosin, which can cause confusion and sedation but was apparently not experienced previously in this patient. Blood alcohol level was negative [174].

3.5.1.HDJ Ketoconazole

1J) Interaction Effect: decreased chlordiazepoxide clearance and potentially increased chlordiazepoxide toxicity (excessive sedation and prolonged hypnotic effects)

2J) Summary: Chlordiazepoxide clearance was reduced when administered with ketoconazole[129]. Potential exist for increased chlordiazepoxide concentrations and subsequent chlordiazepoxide toxicity (excessive sedation and prolonged hypnotic effects).

3J) Severity: moderate

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: Concurrent use of chlordiazepoxide and ketoconazole decreases chlordiazepoxide clearance. Monitor for increased chlordiazepoxide toxicity (excessive sedation and prolonged hypnotic effects).

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Chlordiazepoxide clearance was reduced in a study evaluating the pharmacokinetics of chlordiazepoxide after a single dose of ketoconazole and after a 5-day course of ketoconazole given to healthy subjects. Six subjects received oral ketoconazole 200 mg or 400 mg with chlordiazepoxide 0.6 mg/kg injected intravenously over 5 minutes. After the single dose of ketoconazole, chlordiazepoxide clearance decreased by 20% and volume of distribution by 26%. After 5 days of ketoconazole therapy in 5 subjects, chlordiazepoxide clearance was reduced by 38% and lower concentrations of its metabolite N-desmethylchlordiazepoxide were found. Concentrations of the metabolite demoxepam were unchanged. The postulated mechanism of this interaction was partial inhibition by ketoconazole of hepatic oxidative metabolism of chlordiazepoxide and its metabolites [129].

3.5.1.HEJ Ketoconazole

1J) Interaction Effect: increased risk for QT prolongation

2J) Summary: Caution is advised when using amitriptyline together with oral ketoconazole as both agents are known to prolong the QT interval[506][507]. Concomitant use may result in additive effects on the QT interval, increasing the risk for serious ventricular arrhythmias, including torsades de pointes.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Caution is advised when using amitriptyline together with oral ketoconazole as both agents are known to prolong the QT interval[506][507]. Concomitant use may result in additive effects on the QT interval, increasing the risk for serious ventricular arrhythmias, including torsades de pointes.

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.HF] Ketoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.HG] Ketorolac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.HH] Lacosamide

- 1) Interaction Effect: increased risk of PR interval prolongation, [atrioventricular block](#), or bradycardia
- 2) Summary: Lacosamide has been associated with PR-interval prolongation. Coadministration with another drug known to prolong the PR interval should be undertaken with caution due to the risk of additive effects on the PR interval that can lead to serious cardiac adverse effects, including [atrioventricular block](#) or bradycardia. If concurrent use is required obtain ECG prior to treatment and following dose titration. Monitoring is of particular importance if lacosamide is administered via IV route[125].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Lacosamide has been associated with PR-interval prolongation. Coadministration with another drug known to prolong the PR interval should be undertaken with caution due to the risk of additive effects on the PR interval that can lead to serious cardiac adverse effects, including [atrioventricular block](#) or bradycardia. If concurrent use is required obtain ECG prior to treatment and following dose titration. Monitoring is of particular importance if lacosamide is administered via IV route[125].
- 7) Probable Mechanism: additive effects on PR interval prolongation

3.5.1.HI] Lapatinib

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [amitriptyline](#) and lapatinib concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[300].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [amitriptyline](#) and lapatinib concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[300].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.HJ] 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[984][985][986]. 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[984][985][986].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.HK] Levalbuterol

- 1) Interaction Effect: an increased risk of cardiovascular system effects (eg, [tachycardia](#), blood pressure changes)
- 2) Summary: [Levalbuterol](#) should be administered with extreme caution to patients being treated with tricyclic antidepressants (TCAs), or within 2 weeks of TCA discontinuation, because the action of [albuterol](#)

on the vascular system may be potentiated. Consider alternative therapy in patients using TCAs[1002]. If concomitant administration is required, monitor the patient closely.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Levalbuterol](#) should be administered with extreme caution to patients being treated with tricyclic antidepressants (TCAs), or within 2 weeks of TCA discontinuation. Concomitant use of [levalbuterol](#) and TCAs may potentiate the action of [albuterol](#) on the vascular system. Consider alternative therapy in patients using TCAs[1002]. If concomitant administration is required, monitor the patient closely.

7J) Probable Mechanism: potentiation of vascular effects

3.5.1.HLJ [Levofloxacin](#)

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

2J) 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[554].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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[554].

7J) Probable Mechanism: additive effects on QT interval

3.5.1.HMJ [Levomethadyl](#)

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

2J) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as [amitriptyline](#) that prolong the QT interval[301].

3J) Severity: contraindicated

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: Levomethadyl is contraindicated in patients being treated with [amitriptyline](#) as it may precipitate QT prolongation and interact with levomethadyl.

7J) Probable Mechanism: unknown

3.5.1.HNJ [Levomilnacipran](#)

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

2J) 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[555].

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[555].

7) Probable Mechanism: additive serotonergic effects

3.5.1.HO| [Levonorgestrel](#)

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b)) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c)) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d)) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e)) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f)) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g)) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.HP] Levorphanol

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.HQ] Levothyroxine

- 1) Interaction Effect: increased therapeutic and toxic effects of both [levothyroxine](#) and tricyclic antidepressant
- 2) Summary: Coadministration of [levothyroxine](#) and a tricyclic antidepressant (TCA) may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of [cardiac arrhythmias](#) and CNS stimulation. The onset of action for the TCA may also be accelerated[927]. If coadministration is necessary, monitor the patient and consider adjusting the timing or dosage of one or both of the drugs.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [levothyroxine](#) and a tricyclic antidepressant (TCA), as it may increase the therapeutic and toxic effects of both drugs. Toxic effects may include increased risk of [cardiac arrhythmias](#) and CNS stimulation. The onset of action for the TCA may also be accelerated[927]. If concomitant use is required, monitor the patient and consider adjusting the timing or dosage of one or both of the drugs.
- 7) Probable Mechanism: increased receptor sensitivity to catecholamines

3.5.1.HR] Lidoflazine

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) and lidoflazine have been shown to prolong the QTc interval at the recommended therapeutic dose[970][971]. Even though no formal drug interaction studies

have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as lidoflazine, is not recommended [972].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of lidoflazine and tricyclic antidepressants is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HS] Linezolid

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

2) Summary: In a review of post-marketing data, serotonin toxicity was reported with concurrent use of [linezolid](#) and [amitriptyline](#), either alone or in combination with other serotonergic agents[625]. Although coadministration of [linezolid](#) and serotonergic agents did not result in [serotonin syndrome](#) in phase 1, 2, or 3 clinical trials, [linezolid](#) is a reversible, non-selective MAOI and can potentially interact with serotonergic agents, precipitating the [serotonin syndrome](#). If concurrent use of [linezolid](#) and a serotonergic agent is clinically warranted, monitor patients closely for signs and symptoms of [serotonin syndrome](#), such as cognitive dysfunction, [hyperpyrexia](#), hyperreflexia, and incoordination. Consider discontinuing either one or both agents if these symptoms occur, keeping in mind that discontinuation of the concomitant serotonergic agent may result in associated discontinuation symptoms [624].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Serotonin toxicity has been reported with concurrent use of [linezolid](#) and [amitriptyline](#), either alone or in combination with other serotonergic agents. If concurrent use of [linezolid](#) and [amitriptyline](#) is clinically necessary, monitor patients closely for signs and symptoms of [serotonin syndrome](#), such as cognitive dysfunction, [hyperpyrexia](#), hyperreflexia, and incoordination. Consider discontinuing either one or both agents if these symptoms occur, keeping in mind that discontinuation of the concomitant serotonergic agent may result in associated discontinuation symptoms[624].

7) Probable Mechanism: additive serotonergic activity

8) Literature Reports

a) In a review of post-marketing data, 3 cases of serotonin toxicity were reported in the concurrent use of [amitriptyline](#) and [linezolid](#). A review was conducted of post-marketing adverse events reported to the US Food and Drug Administration's Adverse Event Reporting System (AERS) database between November 1997 and September 2003 regarding serotonin toxicity with [linezolid](#) use. A serotonin toxicity case was defined as having: (a) [linezolid](#) as the primary suspect drug, (b) concomitant administration of 1 or more secondary suspect drug with CNS serotonergic activity, and (c) serotonin toxicity, as defined by the modified Hunter Serotonin Toxicity Criteria or by the reporter of the adverse event. A total of 29 cases were identified (age range 17 to 83 years), where [linezolid](#) was used concomitantly with 1 drug (n=20), with 2 drugs (n=6), and with 3 or more drugs (n=3). While SSRIs were the most common class of drugs received concomitantly with [linezolid](#) (n=26), other drug classes included tricyclic antidepressants (n=6), and atypical antidepressants (n=4). Additionally, drugs used concurrently included [carbidopa-levodopa](#) (n=2), [dextromethorphan](#) (n=1), [lithium](#) (n=1), [metoclopramide](#) (n=1), [risperidone](#) (n=1), and [tramadol](#) (n=1). Symptoms of serotonin toxicity included tremor, fever, seizure, clonus, sweating, agitation, akathisia, rigors, twitching, and muscle rigidity. Intervention including hospitalization was required in 13 patients, and 3 deaths were reported with concurrent SSRI use. Among the

6 cases involving concurrent use of [linezolid](#) and tricyclic antidepressants, 3 patients received [amitriptyline](#), either alone (n=1), or in combination with [metoclopramide](#) (n=1) or [paroxetine](#) and [trazodone](#) (n=1) [625].

3.5.1.HT] [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[721].
- 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[721].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.HU] [Lithium](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor, and [lithium](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#)[236]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [lithium](#) 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 [240].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [lithium](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.HV] [Lopinavir](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Avoid using [amitriptyline](#) and [lopinavir/ritonavir](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[299].
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid using [amitriptyline](#) and [lopinavir/ritonavir](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[299].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.HW| Lorcainide

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended[467][468][469].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [465].

b) A 68-year-old man suffering from agitated [major depression](#) was begun on a dose of [desipramine](#) 125 mg daily which produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An increased dose of 175 mg daily produced excellent clinical response with no side effects. He developed [atrial fibrillation and flutter](#). [Digoxin](#) 0.25 mg daily was added to his therapy, and [desipramine](#) was discontinued. His [arrhythmia](#) was suppressed with the addition of [propafenone](#) 150 mg twice daily and 300 mg at bedtime. [Desipramine](#) 150 mg daily was again begun, at which point he experienced dry mouth, sedation, and shakiness; the [desipramine](#) serum level was measured at 2092 nmol/L. The [desipramine](#) was discontinued for five days, the side effects ceased, and [desipramine](#) therapy was resumed at 75 mg daily. The [desipramine](#) serum level was measured at 1130 nmol/L [466].

3.5.1.HX| Lorcaserin

- 1) Interaction Effect: increased [amitriptyline](#) plasma concentrations; increased risk of [serotonin syndrome](#)
- 2) Summary: The concomitant use of [amitriptyline](#), a CYP2D6 substrate[236], and lorcaserin, a CYP2D6 inhibitor, may cause increased [amitriptyline](#) plasma concentrations resulting in increased [amitriptyline](#) adverse effects. Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic neurotransmitter system, such as [amitriptyline](#), may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution [892]. Dose reduction of [amitriptyline](#) may be required when coadministered with lorcaserin, and if lorcaserin therapy is withdrawn, a higher dose of [amitriptyline](#) may be necessary. [Amitriptyline](#) plasma level monitoring may be desirable with coadministration [236].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with the concomitant use of [amitriptyline](#) with lorcaserin as this may cause increased [amitriptyline](#) plasma concentrations and may also result in additive serotonergic effects, increasing the risk of [serotonin syndrome](#)[892]. If concomitant use is required, dose reduction may be warranted for [amitriptyline](#). If lorcaserin therapy is withdrawn, a higher dose of [amitriptyline](#) may be necessary. [Amitriptyline](#) plasma level monitoring may be desirable with coadministration [236].

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

3.5.1.HY] Lornoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.HZ] Loxapine

1) Interaction Effect: potentiation of impaired cognitive function and motor skills and an increased risk of [respiratory depression](#), hypotension, oversedation, and syncope

2) Summary: Concomitant use of [loxapine](#), a CNS depressant, and other CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of [respiratory depression](#), hypotension, oversedation, and syncope. If [loxapine](#) and other CNS depressants are used concurrently, consider a dose reduction of the CNS depressant[204] and use with caution [205].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [loxapine](#) and other CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of [respiratory depression](#), hypotension, oversedation, and syncope. If [loxapine](#) and CNS depressants are used concurrently, consider a dose reduction of the CNS depressant[204] and use with caution [205].

7) Probable Mechanism: additive CNS depression

3.5.1.IA] Loxoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.IB] Lumefantrine

- 1) Interaction Effect: an increased risk of QT-interval prolongation
- 2) Summary: Avoid concomitant use of [amitriptyline](#) and artemether/lumefantrine due to the additive risk of QT-interval prolongation. Coadministration of artemether/lumefantrine, a CYP2D6 inhibitor, may cause plasma concentrations of [amitriptyline](#), a CYP2D6 substrate, to significantly increase and further heighten the risk of QT-interval prolongation or other serious adverse effects. If concurrent administration of [amitriptyline](#) and artemether/lumefantrine is medically required, use caution and monitor the ECG. 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)[534].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of [amitriptyline](#) and artemether/lumefantrine due to the additive risk of QT-interval prolongation and adverse effects. If concurrent administration of [amitriptyline](#) and artemether/lumefantrine is medically required, use caution and monitor the ECG. 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)[534].
- 7) Probable Mechanism: additive effects on QT-interval prolongation; inhibition of CYP2D6-mediated metabolism of [amitriptyline](#)

3.5.1.IC] Lumiracoxib

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.ID] Magnolia

- 1) Interaction Effect: increased central nervous system depression
- 2) Summary: Magnolia bark constituents magnolol and honokiol exert central nervous system depression in animals[182][183][184]. Effects are likely to be of short duration with a half-life of 49 to 56 minutes observed in rats [185]. The effects of honokiol, an active constituent of magnolia, were reversed following administration of [flumazenil](#) [186]. Therefore, the central nervous system activity of magnolia may be similar to that of benzodiazepines. Caution is advised if magnolia bark and a benzodiazepine are taken concomitantly, as the patient may experience excessive central nervous system depression.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: If patients elect to take these compounds concomitantly, they should avoid operating heavy machinery or driving until the magnitude of the effect is known.
- 7) Probable Mechanism: possibly stimulation of GABA-A receptors
- 8) Literature Reports

a) Honokiol, a neolignane derivative present in magnolia bark, has central nervous system depressant activity and at lower doses, anxiolytic activity. Anxiolytic activity (as shown by prolonged time spent in the open arms of the maze) was noted in a plus-maze test in mice of a single oral dose of 20 milligrams/kilogram (mg/kg) honokiol (p less than 0.05). Honokiol did not affect traction performance, whereas [diazepam](#) 0.5 mg/kg to 2 mg/kg prolonged time spent in open arms of the maze and disrupted traction performance. After 7 days of treatment with 0.2 mg/kg honokiol and after a single treatment with 1 mg/kg [diazepam](#), performance in the plus-maze was nearly equivalent. The effect of honokiol was reversed following subcutaneous administration of [flumazenil](#) 0.3 mg/kg. Combination treatment with honokiol and [diazepam](#) significantly prolonged the time spent in open arms of the maze over treatment with either alone (p less than 0.05). Honokiol reduced the effect of [diazepam](#) on motor activity, but did not affect diazepam-induced inhibition of traction performance. The authors concluded based on their findings that honokiol induces an anxiolytic effect with less liability of causing sedation, disinhibition, or motor dysfunction than [diazepam](#). Possible mechanisms proposed were that honokiol selectively stimulates GABA-A receptors, or honokiol binds to other sites related to the anxiolytic effect [177].

b)) Honokiol administered intravenously to 5 rats resulted in an elimination rate constant of 0.08 ± 0.01 Liters/minute (L/minute) after a 5 mg/kg loading dose, and 0.06 ± 0.02 L/minute after a 10 mg/kg loading dose. Half-life was 49.22 ± 6.78 minutes after a 5 mg/kg loading dose, and 56.24 ± 7.30 minutes after a 10 mg/kg loading dose. The bioavailability as expressed as area under the curve (AUC) was 58.87 ± 4.19 micrograms/milliliter/minute (mcg/mL/minute) after a 5 mg/kg loading dose, and 133.89 ± 16.26 mcg/mL/minute (p less than 0.05) after a 10 mg/kg loading dose [178].

c)) Magnolol and honokiol at 100 mg/kg, 200 mg/kg, and 400 mg/kg administered intraperitoneally to mice suppressed grip strength in a dose-dependent manner. Grip strength was lost within 30 minutes, which was sustained for 3 hours after a 400 mg/kg dose of either compound. Spinal reflexes in the chick were inhibited in a dose-dependent manner with magnolol and honokiol at 12.5 mg/kg, 25 mg/kg, 50 mg/kg, and 100 mg/kg intraperitoneally [179].

d)) Magnolol and honokiol may cause depression of the ascending activating systems and the spinal cord based on mice studies demonstrating sedation, ataxia, muscle relaxation, and anticonvulsant activities of magnolol and honokiol. Magnolol at 63 mg/kg intraperitoneally produced [hypomotility](#), [ptosis](#), and sedation. Magnolol 125 mg/kg produced sedation, ataxia, and muscle relaxation; at 250 mg/kg magnolol produced ataxia, loss of righting reflex, and muscle relaxation of 4 legs. Honokiol produced similar effects at 125 mg/kg, 250 mg/kg, and 500 mg/kg. Both magnolol and honokiol compounds at 50 mg/kg suppressed spinal reflexes in chicks. In mice, pretreatment with magnolol 100 mg/kg inhibited tonic extensor convulsion and death induced by an intracerebroventricular injection of [penicillin G](#) potassium 50 micrograms (mcg) [180].

e)) The ether extract of magnolia bark and its purified constituents, magnolol and honokiol were examined in terms of muscle relaxant properties in the mouse model. Magnolol at 100 mg/kg produced muscle relaxation for 2 hours; magnolol 250 mg/kg induced loss of righting reflex and muscle relaxation extending beyond 3 hours. Honokiol 250 mg/kg exhibited muscle relaxation properties for 3 hours with 500 mg/kg producing loss of righting reflex. Muscle relaxing properties of both compounds subsided fully within 24 hours after injection. The ether extract at 1 gram/kg induced loss of righting reflex 30 minutes after injection for nearly 60 minutes [181].

3.5.1.IE] [Meclizine](#)

1)) Interaction Effect: an increase in CNS or [respiratory depression](#)

2)) Summary: Concomitant use of [meclizine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives may potentiate CNS depression cognitive and motor effects. Avoid concurrent use of alcohol while taking [meclizine](#)[198][199][200] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [meclizine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may potentiate CNS depression. Avoid concurrent use of alcohol with [meclizine](#)[198][199][200] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.

7)) Probable Mechanism: additive CNS depression

3.5.1.IF] [Meclofenamate](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.IG] [Medroxyprogesterone Acetate](#)

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes
- 8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much

as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.IH] [Mefenamic Acid](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.II] [Mefloquine](#)

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

2) Summary: Use caution when using [amitriptyline](#) and [mefloquine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[298].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when using [amitriptyline](#) and [mefloquine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[298].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.IJ] [Meloxicam](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436].

When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.IK] [Meperidine](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].

7) Probable Mechanism: additive CNS depression

8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.IL] [Meperidine](#)

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

2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor, and [meperidine](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#)[236]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [meperidine](#)

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 [240].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [meperidine](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

3.5.1.IM] Mephenesin

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[216][217][218][219].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

3.5.1.IN] Mephobarbital

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[142][143][144][145][146].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [133][134][135][136][137].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [138]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [139]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [140]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [141].

3.5.1.IO] Mephobarbital

- 1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
- 2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
- 7) Probable Mechanism: increased tricyclic antidepressant metabolism
- 8) Literature Reports

a) The pharmacokinetics of a single oral dose of **desipramine** (100 mg) were studied in eight epileptic patients chronically treated with **phenobarbital** and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma **desipramine** concentrations (74 nmol/L vs. 107 nmol/L), smaller **desipramine** area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter **desipramine** elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.IP] Meprobamate

- 1) Interaction Effect: additive **respiratory depression**
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[216][217][218][219].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for **respiratory depression** when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.IQ] 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**[454].
- 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](#)[454].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.IR] [Mestranol](#)

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.IS] [Metaxalone](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[216][217][218][219].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.IT] [Methadone](#)

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Concomitant use of [methadone](#), which is a CNS depressant, with another CNS depressant may result in additive effects including [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. If [methadone](#) is coadministered with a CNS depressant, initiate the dose of [methadone](#) at 2.5 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[124].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [methadone](#), which is a CNS depressant, with another CNS depressant may result in additive effects including [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. If [methadone](#) is coadministered with a CNS depressant, initiate the dose of [methadone](#) at 2.5 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[124].
- 7) Probable Mechanism: additive CNS depression effects

3.5.1.IU] [Methadone](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [amitriptyline](#) and [methadone](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[290].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [amitriptyline](#) and [methadone](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[290].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.IV] [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[721].
- 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[721].

7) Probable Mechanism: additive serotonergic effect

3.5.1.IW] [Methocarbamol](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[216][217][218][219].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

3.5.1.IX] [Methohexital](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[142][143][144][145][146].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [133][134][135][136][137].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [138]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [139]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [140]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [141].

3.5.1.IY] [Methohexital](#)

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.

- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
- 7) Probable Mechanism: increased tricyclic antidepressant metabolism
- 8) Literature Reports

a) The pharmacokinetics of a single oral dose of **desipramine** (100 mg) were studied in eight epileptic patients chronically treated with **phenobarbital** and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma **desipramine** concentrations (74 nmol/L vs. 107 nmol/L), smaller **desipramine** area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter **desipramine** elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.IZ] **Methoxamine**

- 1) Interaction Effect: **hypertension**, **cardiac arrhythmias**, and **tachycardia**
- 2) Summary: Concomitant use of local anesthetic solutions containing **epinephrine** to patients receiving a tricyclic antidepressant may produce severe, prolonged **hypertension** and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of **epinephrine** may be potentiated by tricyclic antidepressants [416] Clinical trials have demonstrated a 2- to 8-fold increase in the effects of **IV infusions** of alpha-adrenergic drugs to volunteers on tricyclic antidepressants. **Arrhythmias** and other severe adverse effects have also been reported [419][420][421][422].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of local anesthetic solutions containing **epinephrine** to patients receiving a tricyclic antidepressant may produce severe, prolonged **hypertension** and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of **epinephrine** may be potentiated by tricyclic antidepressants [416]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
- 7) Probable Mechanism: inhibition of **norepinephrine** reuptake
- 8) Literature Reports

a) Four healthy volunteers received **IV infusions** of various sympathomimetic amines (**epinephrine**, **norepinephrine**, **phenylephrine**, and **isoproterenol**) before and after **imipramine** (25 mg 3 times daily for 5 days). They showed an increased pressor response to **epinephrine** (2- to 4-fold), **norepinephrine** (4- to 8-fold), and **phenylephrine** (2- to 3-fold) after **imipramine**, but no difference was observed in the response to **isoproterenol**. Thus, the increased pressor response appeared to occur only for alpha-adrenergic effects. All 4 subjects demonstrated changes in cardiac rhythm with **epinephrine** and **imipramine** consisting of sinus **arrhythmia** in 3 subjects and multiple **ectopic beats** and a **nodal rhythm** in the fourth subject [417].

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients who received a local anesthetic with **norepinephrine** (1:25,000) had severe

reactions (severe headaches, chest tightness, [subarachnoid hemorrhage](#)). The drug history was incomplete, but at least 3 had been taking a tricyclic antidepressant at the time [418].

3.5.1.JA| [Methyldopa](#)

- 1) Interaction Effect: blood pressure elevation
- 2) Summary: The majority of patients taking [methyldopa](#) and a tricyclic antidepressant show no adverse hypertensive effects, although loss of antihypertensive efficacy has been reported[569].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor blood pressure carefully during concurrent therapy; consider use of alternative antihypertensive agent if more conventional agents (ACE inhibitors, [calcium](#) antagonists) are not already being used. Tricyclic antidepressants generally are not effective in relieving [drug-induced depression](#) which may be encountered with [methyldopa](#).
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A hypertensive patient who was previously well controlled on [methyldopa](#) developed blood pressure elevation when [amitriptyline](#) therapy was initiated [564]. Following 10 days of therapy, the patient became agitated, developed a fine hand tremor, and "felt like a different person". However, these adverse CNS effects have been reported with both drugs and there is no evidence they were due to an adverse interaction between [methyldopa](#) and tricyclic antidepressants [565] [566][567][568].

3.5.1.JB| [Methylene Blue](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) (labile blood pressure, [hyperthermia](#), neuromuscular abnormalities, mental status changes, gastrointestinal symptoms)
- 2) Summary: Concurrent use of [amitriptyline](#) and methylene blue (an MAOI) is contraindicated[773]. Concurrent administration may result in potentially fatal [serotonin syndrome](#) [774]. In settings where urgent treatment with methylene blue is not required, discontinue [amitriptyline](#) at least 14 days prior to initiating treatment with methylene blue. If no alternative pharmacological or non-pharmacological treatment is available and urgent treatment with methylene blue is required in a patient on [amitriptyline](#) therapy, and the potential benefits outweigh the risk of [serotonin syndrome](#), [amitriptyline](#) must be discontinued immediately [775]. Use lowest possible dose of methylene blue [774]. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. [Amitriptyline](#) may be resumed 24 hours after the last dose of methylene blue has been given [775].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [amitriptyline](#) and methylene blue (an MAOI) is contraindicated[773]. Concurrent administration may result in potentially fatal [serotonin syndrome](#) [774]. In settings where urgent treatment with methylene blue is not required, discontinue [amitriptyline](#) at least 14 days prior to initiating treatment with methylene blue. If no alternative pharmacological or non-pharmacological treatment is available and urgent treatment with methylene blue is required in a patient on [amitriptyline](#) therapy, and the potential benefits outweigh the risk of [serotonin syndrome](#), [amitriptyline](#) must be discontinued immediately [775]. Use lowest possible dose of methylene blue [774]. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of methylene blue has

been administered, whichever comes first. [Amitriptyline](#) may be resumed 24 hours after the last dose of methylene blue has been given [775].

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

8J) Literature Reports

- aJ) There have been reports of serious reactions, including hypertensive crises, severe convulsions, and death, in patients receiving concomitant tricyclic antidepressants and MAOIs [773].

3.5.1.JC| [Metoclopramide](#)

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

2J) Summary: Concomitant use of [metoclopramide](#) with tricyclic antidepressants may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated[570]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions. Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [571].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of tricyclic antidepressant with [metoclopramide](#) is contraindicated[570]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#). Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [571].

7J) Probable Mechanism: unknown

3.5.1.JD| [Metronidazole](#)

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

2J) 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[292].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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[292].

7J) Probable Mechanism: additive QT-interval prolongation

8J) Literature Reports

- aJ) 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 [292].

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 [293].

3.5.1.JE] Midodrine

- 1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
- 2) Summary: Concomitant use of local anesthetic solutions containing epinephrine to patients receiving a tricyclic antidepressant may produce severe, prolonged hypertension and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of epinephrine may be potentiated by tricyclic antidepressants [416] Clinical trials have demonstrated a 2- to 8-fold increase in the effects of IV infusions of alpha-adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported [419][420][421][422].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of local anesthetic solutions containing epinephrine to patients receiving a tricyclic antidepressant may produce severe, prolonged hypertension and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of epinephrine may be potentiated by tricyclic antidepressants [416]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
- 7) Probable Mechanism: inhibition of norepinephrine reuptake
- 8) Literature Reports

a) Four healthy volunteers received IV infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg 3 times daily for 5 days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha-adrenergic effects. All 4 subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in 3 subjects and multiple ectopic beats and a nodal rhythm in the fourth subject [417].

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients who received a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least 3 had been taking a tricyclic antidepressant at the time [418].

3.5.1.JF] Mifepristone

- 1) Interaction Effect: increased exposure to amitriptyline

2) Summary: Concomitant administration of [amitriptyline](#), a CYP2C9 substrate, with [mifepristone](#), a CYP2C9 inhibitor, may lead to increased exposure to [amitriptyline](#). Although not specifically studied with [amitriptyline](#), coadministration of a single 40 mg [fluvastatin](#) dose (a CYP2C8/2C9 substrate) in healthy subjects receiving [mifepristone](#) (Korlym(TM)) 1200 mg orally once daily led to significantly increased [fluvastatin](#) exposure, with geometric mean ratios (with/without coadministration) of [fluvastatin](#) AUC and Cmax of 3.57 and 1.76, respectively. The lowest dose of [amitriptyline](#) should be used when given concomitantly with [mifepristone](#) (Korlym(TM)) and patients should be monitored closely for [amitriptyline](#) adverse effects. Due to the long terminal half-life of [mifepristone](#) after reaching steady state, allow at least 2 weeks following cessation of [mifepristone](#) (Korlym(TM)) before increasing the dose of [amitriptyline](#)[446].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: When using [amitriptyline](#) together with [mifepristone](#), use the lowest possible dose of [amitriptyline](#) and monitor patients closely for adverse effects as concomitant use may lead to increased exposure to [amitriptyline](#). Due to the long terminal half-life of [mifepristone](#) after reaching steady state, allow at least 2 weeks following cessation of [mifepristone](#) (Korlym(TM)) before increasing the dose of [amitriptyline](#)[446].

7) Probable Mechanism: inhibition of CYP2C9-mediated metabolism of [amitriptyline](#)

3.5.1.JG| Milnacipran

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

2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[236], and milnacipran, a selective serotonin and [norepinephrine](#) reuptake inhibitor, affect the serotonergic neurotransmitter systems. Concomitant use is not recommended due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#) [433]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and milnacipran 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 [240].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of [amitriptyline](#) and milnacipran may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. Therefore, coadministration of [amitriptyline](#) and milnacipran is not recommended [433]. If concomitant therapy is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

3.5.1.JH| Mirabegron

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

2) Summary: Patients concurrently treated with mirabegron, a moderate CYP2D6 inhibitor[572], and [amitriptyline](#), a CYP2D6 substrate [236], may have an increase in [amitriptyline](#) exposure and risk of adverse events. Concomitant use of tricyclic antidepressants with CYP2D6 inhibitors may require

lower doses for either the tricyclic antidepressant or the CYP2D6 inhibitor; monitoring of the tricyclic antidepressant is recommended [236].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of mirabegron, a moderate CYP2D6 inhibitor[572], and amitriptyline, a CYP2D6 substrate [236], may result in increased amitriptyline exposure. Concomitant use of tricyclic antidepressants with CYP2D6 inhibitors may require lower doses for either the tricyclic antidepressant or the CYP2D6 inhibitor; monitoring of the tricyclic antidepressant is recommended [236].

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

3.5.1.JI] Mirtazapine

1) Interaction Effect: increased risk of CNS depression

2) Summary: Concomitant use of mirtazapine and any benzodiazepine may result in additive CNS depressive effects. When diazepam was coadministered with mirtazapine in 12 healthy patients, diazepam had minimal effects on plasma levels of mirtazapine. However, because motor-skill impairment is additive, concomitant use should be avoided[132].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of mirtazapine and any benzodiazepine should be avoided due to additive CNS depression[132].

7) Probable Mechanism: additive CNS depression

8) Literature Reports

a) When diazepam 15 mg was coadministered with mirtazapine 15 mg in 12 healthy patients, diazepam had minimal effects on plasma levels of mirtazapine. However impaired motor skills is additive [132].

3.5.1.JJ] 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[423]. 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 [240].

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[423].

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 [424].

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 [425].

3.5.1.JK| Moclobemide

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

2)) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[269][270][271][272]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [273]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [274].

3)) Severity: contraindicated

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.

7)) Probable Mechanism: altered catecholamine uptake and metabolism

8)) Literature Reports

a)) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [251][252][253][254][255][256]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [257].

b)) The development of [serotonin syndrome](#) was reported due to administration of a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received

clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [258].

c) A drug interaction was reported when a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [259].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [260].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [261].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranlycypromine](#) in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to [disseminated intravascular coagulation](#) and eventual death [262].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranlycypromine](#) in any combination, and d) close monitoring of patients [263][253][254][264][265]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [266]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [266]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [267][254][268].

3.5.1.JL] [Moricizine](#)

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

2) Summary: Concomitant use of tricyclic antidepressants, including [amitriptyline](#), and class IA antiarrhythmics, including [moricizine](#), may increase the risk of [cardiotoxicity](#) due to similar cardiac effects of these drugs[232][233]. Therefore, monitoring the patient for signs and symptoms of [cardiac toxicity](#) during coadministration of [amitriptyline](#) and [moricizine](#) may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [amitriptyline](#) and [moricizine](#) may increase the risk of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs[232][233]. Consider monitoring the patient for signs and symptoms of [cardiac toxicity](#), including any changes in the ECG.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) An increased incidence in sudden death was observed in 6 out of 53 patients with cardiac disease receiving [amitriptyline](#), compared with 0 out of 53 in the control group. It was recommended that [amitriptyline](#) be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful [234][26].

b) In a placebo controlled study, [imipramine](#) 3.5 mg/kg was administered daily to seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed [premature atrial depolarizations](#) and [premature ventricular depolarizations](#) before therapy. One patient had 33 [premature atrial depolarizations](#) (PAD) and 30 [premature ventricular depolarizations](#) (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on [imipramine](#). The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on [imipramine](#). The authors also cautioned that the incidence of [cardiotoxicity](#) may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that [quinidine](#) and [procainamide](#) not be used to treat the [arrhythmias](#) of a tricyclic overdose. The similarities between these agents may exacerbate the [cardiotoxicity](#) [235].

3.5.1.JM] Morniflumate

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.JN] Morphine

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.JO] Morphine Sulfate Liposome

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.JP| Moxifloxacin

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

2J) Summary: **Moxifloxacin** has been associated with QT-interval prolongation. Coadministration with another drug known to prolong the QT-interval should be avoided because of risk for additive effects on the QT-interval that can lead to serious cardiac adverse effects, including **torsade de pointes**. Elderly patients receiving treatment with IV **moxifloxacin** may be at an increased risk for QT prolongation. If concurrent use is not avoidable, do not exceed the recommended dose or infusion rate of **moxifloxacin**[937] and monitor for changes in the QT-interval.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: **Moxifloxacin** has been associated with QT-interval prolongation. Coadministration with another drug known to prolong the QT-interval should be avoided because of risk for additive effects on the QT-interval that can lead to serious cardiac adverse effects, including **torsade de pointes**. Elderly patients receiving treatment with IV **moxifloxacin** may be at an increased risk for QT prolongation. If concurrent use is not avoidable, do not exceed the recommended dose or infusion rate of **moxifloxacin**[937] and monitor for changes in the QT-interval.

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

3.5.1.JQ| Nabumetone

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including **intracranial hemorrhage** within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including **intracranial hemorrhage**[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.JR| 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[984][985][986].

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[984][985][986].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.JS] [Naproxen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.JT] [Naratriptan](#)

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

2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor, and [naratriptan](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#)[445][236]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [naratriptan](#) 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 [240].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [naratriptan](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[445][236]. If coadministration is required, appropriate monitoring may be warranted.

7J) Probable Mechanism: additive serotonergic effect

3.5.1.JU] [Nefazodone](#)

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

2J) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[236], and [nefazodone](#), a serotonin and [norepinephrine](#) reuptake inhibitor [432], affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#) [432][236]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [nefazodone](#) 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 [240].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [nefazodone](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[432][236]. If coadministration is required, appropriate monitoring may be warranted.

7J) Probable Mechanism: additive serotonergic effect

3.5.1.JV] [Nefopam](#)

1J) Interaction Effect: an increased risk of seizures

2J) Summary: Nefopam inhibits the neuronal uptake of [norepinephrine](#) and serotonin and increases the risk of seizures, especially in patients with a history of a convulsive disorder. Tricyclic antidepressants also lower the seizure threshold. Therefore, the manufacturer of nefopam advises caution in patients on concurrent tricyclic antidepressant therapy[563].

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: Because of the increased risk of seizures, extreme caution should be exercised in patients receiving nefopam and a tricyclic antidepressant. An alternative analgesic may be considered.

7J) Probable Mechanism: additive lowering of seizure threshold

3.5.1.JW] [Nepafenac](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6j) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.JX] Nialamide

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

2j) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[690][691][692][693]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [694]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [695].

3j) Severity: contraindicated

4j) Onset: delayed

5j) Substantiation: probable

6j) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.

7j) Probable Mechanism: altered catecholamine uptake and metabolism

8j) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [672][673][674][675][676][677]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [678].

b) [Serotonin syndrome](#) occurred in two patients administered a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [679].

c) A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months and subsequently switched to moclobemide 300 mg daily. . The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [680].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [681].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [682].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranlycypromine](#) in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexial state led to [disseminated intravascular coagulation](#) and eventual death [683].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranlycypromine](#) in any combination, and d) close monitoring of patients [684][674][675][685][686]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [687]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [687]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [688][675][689].

3.5.1.JY] Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.JZ] Nilotinib

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

2) Summary: Avoid using [amitriptyline](#) and nilotinib concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Additionally nilotinib is a CYP2D6 inhibitor[291] and [amitriptyline](#) is a CYP2D6 substrate [236]. Caution is advised when using [amitriptyline](#) with a CYP2D6 inhibitor as lower doses of [amitriptyline](#) and/or concomitant drug may be required. Monitoring of [amitriptyline](#) levels is advised [236]. If concomitant therapy with [amitriptyline](#) and nilotinib is required, closely monitor the patient for QT prolongation [291].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid using [amitriptyline](#) and nilotinib concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[291]. Caution is advised when using [amitriptyline](#), a CYP2D6 substrate with a CYP2D6 inhibitor, such as nilotinib, as lower doses of [amitriptyline](#) and/or concomitant drug may be required. Monitoring of [amitriptyline](#) levels is advised [236]. If concomitant therapy with [amitriptyline](#) and nilotinib is required, closely monitor the patient for QT prolongation [291].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.KA] Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.KB] Nimesulide Beta Cyclodextrin

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.KC] Norelgestromin

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours

of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.KD] [Norepinephrine](#)

1) Interaction Effect: [hypertension](#), [cardiac arrhythmias](#), and [tachycardia](#)

2) Summary: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [416] Clinical trials have demonstrated a 2- to 8-fold increase in the effects of [IV infusions](#) of alpha-adrenergic drugs to volunteers on tricyclic antidepressants. [Arrhythmias](#) and other severe adverse effects have also been reported [419][420][421][422].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [416]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of [norepinephrine](#) reuptake

8) Literature Reports

a) Four healthy volunteers received [IV infusions](#) of various sympathomimetic amines ([epinephrine](#), [norepinephrine](#), [phenylephrine](#), and [isoproterenol](#)) before and after [imipramine](#) (25 mg 3 times daily for 5 days). They showed an increased pressor response to [epinephrine](#) (2- to 4-fold), [norepinephrine](#) (4- to 8-fold), and [phenylephrine](#) (2- to 3-fold) after [imipramine](#), but no difference was observed in the response to [isoproterenol](#). Thus, the increased pressor response appeared to occur only for alpha-adrenergic effects. All 4 subjects demonstrated changes in cardiac rhythm with [epinephrine](#) and [imipramine](#) consisting of sinus [arrhythmia](#) in 3 subjects and multiple [ectopic beats](#) and a [nodal rhythm](#) in the fourth subject [417].

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients who received a local anesthetic with [norepinephrine](#) (1:25,000) had severe reactions (severe headaches, chest tightness, [subarachnoid hemorrhage](#)). The drug history was incomplete, but at least 3 had been taking a tricyclic antidepressant at the time [418].

3.5.1.KE] Norethindrone

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

b) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

c) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to

[clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.KF] [Norfloxacin](#)

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

2) Summary: Concomitant use of [norfloxacin](#) and other QT prolonging drugs, such as [amitriptyline](#)[236], may increase the risk of QT interval prolongation and should be undertaken with caution. Geriatric patients may be particularly sensitive to QT prolongation [471]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amitriptyline](#) and [norfloxacin](#), both drugs that prolong the QT interval, may increase the potential for serious cardiovascular effects and should be undertaken with caution. Geriatric patients may be particularly sensitive to QT prolongation[471]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.

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

3.5.1.KGJ Norgestimate

1J) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2J) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7J) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8J) Literature Reports

aJ) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

bJ) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

cJ) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients

taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

d)) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e)) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f)) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g)) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.KH] [Norgestrel](#)

1)) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))

2)) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[368], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [369]. The effects of the interaction appear to be estrogen dose-related [370] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [371].

3)) Severity: minor

4)) Onset: delayed

5)) Substantiation: probable

6j) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7j) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes

8j) Literature Reports

aj) A study evaluated the qualitative effects of concomitant administration of estrogen and tricyclic antidepressants (TCAs). In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients who received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients who received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side effects including lethargy, coarse tremor and systolic hypotension [359].

bj) A case report demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated [360]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [361].

cj) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study, there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [362].

dj) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [363].

e) Three patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of taking [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [364].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the AUC [365].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [366]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [367].

3.5.1.KI] [Nortriptyline](#)

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

2) Summary: Concomitant use of [amitriptyline](#) and [nortriptyline](#) is not common clinical practice. However if using [amitriptyline](#) and [nortriptyline](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [amitriptyline](#) and [nortriptyline](#) is not common clinical practice. However if using [amitriptyline](#) and [nortriptyline](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.KJ] [Octreotide](#)

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

2) Summary: Tricyclic antidepressants (TCAs) and [octreotide](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[349][350]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [octreotide](#), is not recommended [351].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

- 6) Clinical Management: The concurrent administration of [octreotide](#) and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.KK] [Ofloxacin](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [ofloxacin](#) and [amitriptyline](#) may increase the risk of QT interval prolongation and serious cardiovascular effects and should be undertaken with caution. Because geriatric patients may be particularly sensitive to QT prolongation associated with drug effects, take appropriate precautions when coadministering these drugs to this patient population[558]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [amitriptyline](#) and [ofloxacin](#) may increase the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects and should be undertaken with caution. Because geriatric patients may be particularly sensitive to QT prolongation associated with drug effects, take appropriate precautions when coadministering these drugs to this patient population[558]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.KL] [Ondansetron](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [amitriptyline](#) and [ondansetron](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concomitant use is required, [ECG monitoring](#) is recommended[357].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [amitriptyline](#) and [ondansetron](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concomitant use is required, [ECG monitoring](#) is recommended[357].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.KM] [Oxaprozin](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.KN] Oxilofrine

1) Interaction Effect: [hypertension](#), [cardiac arrhythmias](#), and [tachycardia](#)

2) Summary: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [416] Clinical trials have demonstrated a 2- to 8-fold increase in the effects of [IV infusions](#) of alpha-adrenergic drugs to volunteers on tricyclic antidepressants. [Arrhythmias](#) and other severe adverse effects have also been reported [419][420][421][422].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [416]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of [norepinephrine](#) reuptake

8) Literature Reports

a) Four healthy volunteers received [IV infusions](#) of various sympathomimetic amines ([epinephrine](#), [norepinephrine](#), [phenylephrine](#), and [isoproterenol](#)) before and after [imipramine](#) (25 mg 3 times daily for 5 days). They showed an increased pressor response to [epinephrine](#) (2- to 4-fold), [norepinephrine](#) (4- to 8-fold), and [phenylephrine](#) (2- to 3-fold) after [imipramine](#), but no difference was observed in the response to [isoproterenol](#). Thus, the increased pressor response appeared to occur only for alpha-adrenergic effects. All 4 subjects demonstrated changes in cardiac rhythm with [epinephrine](#) and [imipramine](#) consisting of sinus [arrhythmia](#) in 3 subjects and multiple [ectopic beats](#) and a [nodal rhythm](#) in the fourth subject [417].

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients who received a local anesthetic with [norepinephrine](#) (1:25,000) had severe reactions (severe headaches, chest tightness, [subarachnoid hemorrhage](#)). The drug history was incomplete, but at least 3 had been taking a tricyclic antidepressant at the time [418].

3.5.1.KO] Oxycodone

1) Interaction Effect: increased CNS or [respiratory depression](#)

2) Summary: Concomitant use of [oxycodone](#) with other CNS depressants, such as benzodiazepines, may result in [respiratory depression](#), hypotension, profound sedation, coma, or death. If combined use is necessary, monitor the patient and reduce the dose of one or both medications. Initiate [oxycodone](#) controlled-release formulations at one-third to one-half of the usual dosage[195][196] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [197].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [oxycodone](#) with other CNS depressants, such as benzodiazepines, may result in [respiratory depression](#), hypotension, profound sedation, coma or death. If combined use is necessary, monitor the patient and reduce the dose of one or both medications. Initiate [oxycodone](#) controlled-release formulations at one-third to one-half of the usual dosage[195][196] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [197].
- 7) Probable Mechanism: additive effects

3.5.1.KP] [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[413].
- 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[413].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.KQ] [Oxymetazoline](#)

- 1) Interaction Effect: [increased blood pressure](#)
- 2) Summary: Avoid concomitant use of [oxymetazoline](#) and a tricyclic antidepressant as this may result in [hypertension](#). Choose an alternative to [oxymetazoline](#) if use of the tricyclic antidepressant cannot be discontinued[249].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [oxymetazoline](#) and a tricyclic antidepressant is not recommended as this may result in [hypertension](#). If use of the tricyclic antidepressant is required, an alternative to [oxymetazoline](#) should be chosen[249].
- 7) Probable Mechanism: increased sympathomimetic activity

3.5.1.KR] [Oxymorphone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports
 - a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.KS| [Oxymorphone](#)

- 1) Interaction Effect: increased risk of [paralytic ileus](#); increased risk of respiratory and CNS depression
- 2) Summary: Coadministration of [oxymorphone](#) and an anticholinergic agent may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). If coadministration is clinically necessary, monitor for respiratory or CNS depression[977]. Dose reductions of one or both agents may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of [oxymorphone](#) and an anticholinergic agent may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). If coadministration is clinically necessary, monitor for respiratory or CNS depression[977]. Dose reductions of one or both agents may be warranted.
- 7) Probable Mechanism: unknown; additive respiratory and CNS depressant effects

3.5.1.KT| [Oxyphenbutazone](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.KU] Paliperidone

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Avoid using [amitriptyline](#) and [paliperidone](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[395].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid using [amitriptyline](#) and [paliperidone](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[395].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.KV] 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](#)[470].
- 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](#)[470].
- 7) Probable Mechanism: unknown

3.5.1.KW] 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[393].
- 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[393].
- 7) Probable Mechanism: additive QT effects

3.5.1.KX] Parecoxib

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.KY] Pargyline

- 1) Interaction Effect: [neurotoxicity](#), seizures, or [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[765][766][767][768]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [769]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [770].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.
- 7) Probable Mechanism: altered catecholamine uptake and metabolism
- 8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [747][748][749][750][751][752]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [753].

b)) **Serotonin syndrome** occurred in two patients administered a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and **clomipramine** for the treatment of **obsessive-compulsive disorder**, two subjects developed severe reactions characteristic of **serotonin syndrome**. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent **clomipramine** therapy. After taking the first 100 mg dose of **clomipramine**, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and **arrhythmia**. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with **clomipramine** without adverse effects [754].

c)) A drug interaction occurred in a 76-year old woman who had been taking **clomipramine** 50 mg daily for several months and subsequently switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further **mental impairment**, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for **serotonin syndrome** and were resolved a few days later after discontinuing all antidepressant medications [755].

d)) A 39-year old woman with **bipolar disorder** developed **serotonin syndrome** after **imipramine** was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when **imipramine** was started at 50 mg daily, followed by two dosage increases of **imipramine** to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in **imipramine** to 200 mg per day, the patient developed symptoms of **serotonin syndrome**, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with **chlorpromazine** and symptoms resolved over the next few days without further complications [756].

e)) Three patients with **bipolar disorder** developed manic symptoms while undergoing concurrent therapy with **isocarboxazid** and **amitriptyline**. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [757].

f)) In one case, **clomipramine** 10 mg twice daily was added to a stable regimen of **tranylcypromine** in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexial state led to **disseminated intravascular coagulation** and eventual death [758].

g)) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg **amitriptyline** or its equivalent, 45 mg **phenelzine**, or 60 mg **isocarboxazid**) b) oral administration c) avoidance of **clomipramine**, **imipramine**, **desipramine**, and **tranylcypromine** in any combination, and d) close monitoring of patients [759] [749][750][760][761]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [762]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of **amitriptyline** and **isocarboxazid** is preferred [762]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [763][750][764].

3.5.1.KZ] Paroxetine

1J) Interaction Effect: increased risk of QT interval prolongation; increased risk of [serotonin syndrome](#); increased CYP2D6 substrate exposure

2J) Summary: Coadminister [paroxetine](#) (a CYP2D6 inhibitor) cautiously with drugs that are QT-prolonging, serotonergic CYP2D6 substrates. Monitor for [serotonin syndrome](#) with concurrent use, especially during treatment initiation or dose increases, and immediately discontinue and immediately discontinue [paroxetine](#) and other serotonergic agents if symptoms occur. Dose reduction of either [paroxetine](#) or a CYP2D6 substrate may be required, as Cmax and AUC of a single dose of [desipramine](#) (a CYP2D6 substrate), rose by 2- and 5-fold, respectively, when added to an existing regimen with [paroxetine](#). [Paroxetine](#) is also associated with [ventricular tachycardia](#) and [torsade de pointes](#)[296]; monitor for signs of additive prolongation of the QT interval during concurrent use.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadminister cautiously with drugs that are QT-prolonging, serotonergic CYP2D6 substrates. Monitor for [serotonin syndrome](#) with concurrent use, especially during treatment initiation or dose increases, and immediately discontinue [paroxetine](#) and other serotonergic agents if symptoms occur. Dose reduction of either [paroxetine](#) (a CYP2D6 inhibitor) or a CYP2D6 substrate may be required. [Paroxetine](#) is also associated with [ventricular tachycardia](#) and [torsade de pointes](#)[296]; monitor for signs of additive prolongation of the QT interval during concurrent use.

7J) Probable Mechanism: additive QT-prolonging effects; additive serotonergic effects; inhibition of CYP2D6 substrate metabolism by [paroxetine](#)

8J) Literature Reports

aJ) Following a single dose of [desipramine](#) 100 mg (a CYP2D6 substrate) added to steady state dosing of [paroxetine](#) 20 mg/day, the [desipramine](#) Cmax, AUC, and t(1/2) increased by a mean of 2-, 5-, and 3-fold [296].

3.5.1.LA] Pasireotide

1J) Interaction Effect: increased risk of QT prolongation

2J) Summary: Pasireotide is associated with QT-interval prolongation. In 2 studies, QT prolongation occurred at both therapeutic and supratherapeutic doses of pasireotide. Concomitant administration of pasireotide with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval. ECGs at baseline and at 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents[962].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant administration of pasireotide and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation of the QT interval. ECGs at baseline and 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents[962].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.LB] Passionflower

1J) Interaction Effect: additive CNS depression

2) Summary: In one case report, valerian and passionflower used concurrently with [lorazepam](#) resulted in additive CNS depressive effects. It is postulated that the valerian root and passionflower have additive or synergistic effects on the inhibitory activity of benzodiazepines binding to the [gamma-aminobutyric acid \(GABA\)](#) receptors. It is recommended that patients be asked about herbal product use during intake of personal history[162]. Monitor for increased CNS depressive adverse effects if passionflower is coadministered with a benzodiazepine.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of passionflower and benzodiazepines may result in additive CNS depressive effects. It is recommended that patients be asked about herbal product use during intake of personal history[162]. Monitor for increased CNS depressive adverse effects if passionflower is coadministered with a benzodiazepine.

7) Probable Mechanism: additive effects on the benzodiazepine receptor

8) Literature Reports

a) A case report describes a potentiated CNS depressive effect in a 40-year-old man following concomitant use of [lorazepam](#) with valerian and passionflower. The patient, who had been treating with [lorazepam](#) 2 mg/day for 2 months with no adverse effects, self-administered an infusion of valerian subterranean parts (estimated dose, 300 mg). 2 hours before going to bed for 2 consecutive days. On day 3, he instead ingested 3 oral tablets of dry extract from valerian rhizomes (300 mg/tablet) plus roots and aerial parts of passionflower (380 mg/tablet) at 1 hour intervals before bedtime. Nervousness and mild shaking dissipated after going to bed followed by extreme somnolence. After taking the same dose of the valerian root/passionflower product on day 4, he experienced more severe symptoms including substantial hand shaking, dizziness, and palpitations before bedtime followed by profound somnolence. Upon presentation after 32 hours of experiencing these CNS symptoms, he was observed to have nervousness while speaking and demonstrated anxious behavior without shaking. He had a history of general anxiety disorders and dream disorders. His family history was negative for essential tremor and there were no metabolic, [renal](#), or [hepatic disorders](#), [high blood pressure](#), or drug allergies. Because a drug interaction was suspected, the patient was continued on [lorazepam](#) but withdrawn from valerian and passionflower and symptoms resolved. It is postulated that the valerian root and passionflower have additive or synergistic effects on the inhibitory activity of benzodiazepines binding to the [gamma-aminobutyric acid \(GABA\)](#) receptors [162].

b) Chrysin (5,7-di-OH-flavone), a flavonoid in *Passiflora coerulea*, was identified as a naturally-occurring benzodiazepine receptor ligand in plants obtained from local sources at the Universidad de Buenos Aires [190]. However, in a [high performance liquid chromatography](#) analysis sensitive to a detection limit of 1 part per million (ppm), chrysin could not be detected in an ethanolic extract of aerial parts of *Passiflora coerulea* obtained from the botanical garden of the University of Bologna or in a *Passiflora incarnata* fluid extract prepared according to the Italian Pharmacopoeia, IX edition [191]. *Passiflora coerulea* collected in the wild is sometimes adulterated or substituted with the spurious species *Cucurbitella asperata* [192].

3.5.1.LC] Pazopanib

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

2) Summary: Use caution when using [amitriptyline](#) and pazopanib concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concomitant therapy is warranted, closely monitor ECG and electrolytes ([calcium](#), magnesium, and potassium)[355].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [amitriptyline](#) and pazopanib concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concomitant therapy is warranted, closely monitor ECG and electrolytes ([calcium](#), magnesium, and potassium)[355].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.LD] Peginterferon Alfa-2b

- 1) Interaction Effect: increased plasma concentrations of tricyclic antidepressants metabolized by CYP2D6 and increased risk for toxicities; abrupt toxicity may occur when peginterferon alfa-2b is initiated in patient on a stable dose of a tricyclic antidepressant
- 2) Summary: Coadministration of a tricyclic antidepressant metabolized by CYP2D6 and a CYP2D6 inhibitor (ie, peginterferon alfa-2b) may increase the plasma levels of the tricyclic antidepressant and increase the risk for toxicities. Abrupt toxicity may occur when peginterferon alfa-2b is initiated in a patient on stable doses of tricyclic antidepressants[463]. When healthy subjects were given 50 mg of [desipramine](#) (CYP2D6 substrate) before and after 2 doses of peginterferon alfa-2b 3 mcg/kg, there was a 30% increase in the geometric mean [desipramine](#) AUC (last) compared with administration of [desipramine](#) alone [464]. Lower doses of the tricyclic antidepressant or doses of a CYP2D6 inhibitor (ie, peginterferon alfa-2b) may be required. Additionally, when peginterferon alfa-2b is discontinued, an increased tricyclic antidepressant dose may be required. Monitor levels of tricyclic antidepressants when coadministered with a CYP2D6 inhibitor [463].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of a tricyclic antidepressant metabolized by CYP2D6 and a CYP2D6 inhibitor (ie, peginterferon alfa-2b) may increase the plasma levels of the tricyclic antidepressant and increase the risk for toxicities. Abrupt toxicity may occur when peginterferon alfa-2b is initiated in a patient on stable doses of a tricyclic antidepressant. Lower doses of the tricyclic antidepressant or doses of a CYP2D6 inhibitor (ie, peginterferon alfa-2b) may be required. Additionally, when peginterferon alfa-2b is discontinued, an increased tricyclic antidepressant dose may be required. Monitor levels of tricyclic antidepressants when coadministered with a CYP2D6 inhibitor[463].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of tricyclic antidepressants by peginterferon alfa-2b
- 8) Literature Reports

a) Peginterferon alfa-2b inhibited CYP2D6 activity in a drug interaction study. When healthy subjects were given 50 mg of [desipramine](#) before and after 2 doses of peginterferon alfa-2b 3 mcg/kg, there was a 30% increase in the geometric mean [desipramine](#) AUC (last) compared with administration of [desipramine](#) alone [464].

3.5.1.LE] [Pentamidine](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) and [pentamidine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[437][438]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [pentamidine](#), is not recommended [439].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [pentamidine](#) and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.LF] [Pentazocine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.LG] [Pentazocine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor, and [pentazocine](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#)[236]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [pentazocine](#) 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 [240].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [pentazocine](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

3.5.1.LH] Pentobarbital

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[142][143][144][145][146].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [133][134][135][136][137].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [138]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [139]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [140]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [141].

3.5.1.LI] Pentobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under

the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.LJ] Perflutren Lipid Microsphere

- 1J) Interaction Effect: an increased risk of QT interval prolongation
- 2J) Summary: Perflutren can prolong the QT interval, and serious cardiopulmonary reactions, including fatalities, have been reported during or after administration of perflutren[280]. Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, use caution if perflutren is administered concomitantly with other drugs that prolong the QT interval, such as [amitriptyline](#). If concomitant therapy is required, monitor closely for QT interval prolongation.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Use caution when [amitriptyline](#) and perflutren[280] are administered concomitantly as this may result in additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant therapy is required, monitor closely for QT interval prolongation.
- 7J) Probable Mechanism: additive effects on the QT interval
- 8J) Literature Reports

aJ) 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 [280].

3.5.1.LK] Periciazine

- 1J) Interaction Effect: risk of enhanced CNS depression
- 2J) Summary: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[116][117].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[116][117].
- 7J) Probable Mechanism: additive CNS depression

3.5.1.LL] [Phenelzine](#)

- 1) Interaction Effect: [neurotoxicity](#), seizures, or [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[666][667][668][669]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [670]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [671].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: established
- 6) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.
- 7) Probable Mechanism: altered catecholamine uptake and metabolism
- 8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [648][649][650][651][652][653]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [654].

b) The development of [serotonin syndrome](#) was reported due to administration of a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [655].

c) A drug interaction was reported in which a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [656].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [657].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [658].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranlycypromine](#) in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to [disseminated intravascular coagulation](#) and eventual death [659].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranlycypromine](#) in any combination, and d) close monitoring of patients [660] [650][651][661][662]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [663]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added [591]. Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [663]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [664][651][665].

3.5.1.LM] Phenindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[909][910]. Considerable interindividual differences may be found [911].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: In patients receiving tricyclic antidepressants and oral [anticoagulant therapy](#), the prothrombin time ratio or INR ([international normalized ratio](#)) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of [anticoagulation](#) may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.

7) Probable Mechanism: decreased phenindione metabolism; increased phenindione absorption

8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of [nortriptyline](#) or [amitriptyline](#) resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects [906]. This effect was not observed with [warfarin](#).

b) A single oral dose of bishydroxycoumarin after 8 days of [nortriptyline](#) resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers [907]. The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term [anticoagulant therapy](#) who used concurrent TCAs [908]. TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.LN] [Phenobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[142][143][144][145][146].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [133] [134][135][136][137].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [138]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [139]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [140]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [141].

3.5.1.LO] [Phenobarbital](#)

- 1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
- 2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
- 7) Probable Mechanism: increased tricyclic antidepressant metabolism
- 8) Literature Reports

a) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.LP] Phenprocoumon

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[915][916]. Considerable interindividual differences may be found [917].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: In patients receiving tricyclic antidepressants and oral [anticoagulant therapy](#), the prothrombin time ratio or INR ([international normalized ratio](#)) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of [anticoagulation](#) may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
- 7) Probable Mechanism: decreased phenprocoumon metabolism; increased phenprocoumon absorption
- 8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of [nortriptyline](#) or [amitriptyline](#) resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects [912]. This effect was not observed with [warfarin](#).

b) A single oral dose of bishydroxycoumarin after 8 days of [nortriptyline](#) resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers [913]. The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term [anticoagulant therapy](#) who used concurrent TCAs [914]. TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.LQ] Phenylbutazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.LR] [Phenylephrine](#)

- 1) Interaction Effect: [hypertension](#), [cardiac arrhythmias](#), and [tachycardia](#)
- 2) Summary: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [416]. Clinical trials have demonstrated a 2- to 8-fold increase in the effects of [IV infusions](#) of alpha-adrenergic drugs to volunteers on tricyclic antidepressants. [Arrhythmias](#) and other severe adverse effects have also been reported [419][420][421][422].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[415]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [416]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
- 7) Probable Mechanism: inhibition of [norepinephrine](#) reuptake
- 8) Literature Reports

a) Four healthy volunteers received [IV infusions](#) of various sympathomimetic amines ([epinephrine](#), [norepinephrine](#), [phenylephrine](#), and [isoproterenol](#)) before and after [imipramine](#) (25 mg 3 times daily for 5 days). They showed an increased pressor response to [epinephrine](#) (2- to 4-fold), [norepinephrine](#) (4- to 8-fold), and [phenylephrine](#) (2- to 3-fold) after [imipramine](#), but no difference was observed in the response to [isoproterenol](#). Thus, the increased pressor response appeared to occur only for alpha-adrenergic effects. All 4 subjects demonstrated changes in cardiac rhythm with [epinephrine](#) and [imipramine](#) consisting of sinus [arrhythmia](#) in 3 subjects and multiple [ectopic beats](#) and a [nodal rhythm](#) in the fourth subject [417].

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients who received a local anesthetic with [norepinephrine](#) (1:25,000) had severe reactions (severe headaches, chest tightness, [subarachnoid hemorrhage](#)). The drug history was incomplete, but at least 3 had been taking a tricyclic antidepressant at the time [418].

3.5.1.LS| Phenytoin

- 1) Interaction Effect: alterations in serum [phenytoin](#) concentrations
- 2) Summary: Concurrent [phenytoin](#) use with some benzodiazepines occasionally has led to either increased or decreased serum levels of [phenytoin](#), as well as lowered levels of the benzodiazepine, particularly [clonazepam](#)[222][223][224][225].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients for continuing clinical signs of [phenytoin](#) effectiveness and/or emergence of [phenytoin](#) toxicity. Routine serum [phenytoin](#) serum concentrations should be obtained one week after the addition or withdrawal of benzodiazepine therapy.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) There have been reports of clinical intoxication associated with high [phenytoin](#) serum levels in patients receiving nitrazepam in combination with [phenytoin](#) [221].

3.5.1.LT| Phenytoin

- 1) Interaction Effect: an increased risk of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremor)
- 2) Summary: A few case reports have indicated that [imipramine](#) inhibits [phenytoin](#) metabolism resulting in increased serum [phenytoin](#) concentration[573][574]. Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because [phenytoin](#) is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor therapeutic efficacy of [amitriptyline](#); an increased dose may be required. Serum [phenytoin](#) levels should be obtained when tricyclic antidepressant agents are added to therapy due to the potential for impaired [phenytoin](#) metabolism.
- 7) Probable Mechanism: inhibition of [phenytoin](#) metabolism

3.5.1.LU| Piktetoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.LV] 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](#)[238].
- 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](#)[238].
- 7)) Probable Mechanism: additive effects on the QT interval

3.5.1.LW] 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](#)[644].
- 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](#)[644].
- 7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.LX] Piperazine

- 1)) Interaction Effect: increased exposure of CYP2C19 substrates and increased risk of QT interval prolongation
- 2)) Summary: Concomitant administration of piperazine and QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperazine administration, is contraindicated. Concurrent administration of piperazine (a CYP2C19 inhibitor) and a CYP2C19 substrate may increase the exposure of the CYP2C19 substrate. Due to the long half-life of piperazine, caution is advised[918] when administering a CYP2C19 substrate for up to 3 months after discontinuation of piperazine therapy .
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical

6) Clinical Management: Concomitant administration of piperazine (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 piperazine administration, is contraindicated. Concurrent administration of piperazine (a CYP2C19 inhibitor) and a CYP2C19 substrate may increase the exposure of the CYP2C19 substrate. Due to the long half-life of piperazine, caution is advised[918] when administering a CYP2C19 substrate for up to 3 months after discontinuation of piperazine therapy .

7) Probable Mechanism: inhibition of CYP2C19-mediated metabolism of this drug by piperazine; additive QT interval prolongation

3.5.1.LY] Piroxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.LZ] 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[967].

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[967].

7) Probable Mechanism: additive QT prolongation

3.5.1.MA] Pixantrone

1) Interaction Effect: increased exposure of CYP1A2 substrates

- 2) Summary: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[905].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[905].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism by pixantrone

3.5.1.MB] Posaconazole

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use of posaconazole has been associated with QT interval prolongation and torsade de pointes has been reported on rare occasions with posaconazole therapy. Due to the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects, caution is advised when coadministering posaconazole with other drugs that may prolong the QT interval[780], such as amitriptyline . If concurrent therapy is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when posaconazole is given concomitantly with other drugs that may prolong the QT interval, such as amitriptyline, as this may result in additive effects on the QT interval and an increased risk of serious cardiovascular effects[780]. If concurrent therapy is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.MC] Pranoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including intracranial hemorrhage within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including intracranial hemorrhage[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.MD] Primidone

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[142][143][144][145][146].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [133][134][135][136][137].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [138]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [139]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [140]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [141].

3.5.1.ME] Primidone

- 1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
- 2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
- 7) Probable Mechanism: increased tricyclic antidepressant metabolism
- 8) Literature Reports

a) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak

plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.MF] [Procainamide](#)

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

2) Summary: Concomitant use of tricyclic antidepressants, including [amitriptyline](#), and class IA antiarrhythmics, including [procainamide](#), may increase the risk of [cardiotoxicity](#) due to similar cardiac effects of these drugs[232][233]. Therefore, monitoring the patient for signs and symptoms of [cardiac toxicity](#) during coadministration of [amitriptyline](#) and [procainamide](#) may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [amitriptyline](#) and [procainamide](#) may increase the risk of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs[232][233]. Consider monitoring the patient for signs and symptoms of [cardiac toxicity](#), including any changes in the ECG.

7) Probable Mechanism: additive [cardiac toxicity](#)

8) Literature Reports

a) An increased incidence in sudden death was observed in 6 out of 53 patients with cardiac disease receiving [amitriptyline](#), compared with 0 out of 53 in the control group. It was recommended that [amitriptyline](#) be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful [26]. Additional studies were conducted which further confirmed that [amitriptyline](#) was associated with an increased incidence of sudden death in patients with preexisting cardiac disease [430][431].

b) In a placebo controlled study, [imipramine](#) 3.5 mg/kg was administered daily to seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed [premature atrial depolarizations](#) and [premature ventricular depolarizations](#) before therapy. One patient had 33 [premature atrial depolarizations](#) (PAD) and 30 [premature ventricular depolarizations](#) (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on [imipramine](#). The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on [imipramine](#). The authors also cautioned that the incidence of [cardiotoxicity](#) may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that [quinidine](#) and [procainamide](#) not be used to treat the [arrhythmias](#) of a tricyclic overdose. The similarities between these agents may exacerbate the [cardiotoxicity](#) [235].

3.5.1.MG] [Procarbazine](#)

1) Interaction Effect: [neurotoxicity](#), seizures

2) Summary: Concomitant tricyclic antidepressant and more potent MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. [Procarbazine](#) has relatively weak MAOI actions, so while the potential for drug interactions between tricyclic antidepressants and [procarbazine](#) exists, clinical data

are lacking at this time[483][484]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [485].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) [Procarbazine](#) is primarily used as an antineoplastic agent, but was originally investigated as a monoamine oxidase inhibitor [472]. Animal studies have indicated that [procarbazine](#) is a monoamine oxidase inhibitor (MAOI) [473] but appears to be a relatively weak MAOI in man [472]. Hypertensive reactions may still result from concomitant administration of tricyclic antidepressants, sympathomimetics, and tyramine containing foods [472][474].

b) Concomitant administration of monoamine oxidase (MAO) inhibitors with tricyclic antidepressants has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [475][476][477][478][479][480]. Careful examination of such reports indicate unusual circumstances in most cases such as [parenteral administration](#) of a tricyclic. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [481].

c) [Procarbazine](#) therapy should not begin until 7 days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors [482][472].

3.5.1.MH] [Prochlorperazine](#)

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

2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines[341][342][343]. Other phenothiazines may have similar effects, though no reports are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation [344]. Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic antidepressants were taken together, likely due to inhibition of their metabolism [345][346][347][348].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent administration of a phenothiazine and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive effect on QT interval

3.5.1.MI] [Proglumetacin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436].

When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.MJ] [Promethazine](#)

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

2) Summary: Use caution when using [amitriptyline](#) and [promethazine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when using [amitriptyline](#) and [promethazine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.MK] [Propafenone](#)

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

2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended[467][468][469].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [465].

b)) A 68-year-old man suffering from agitated [major depression](#) was begun on a dose of [desipramine](#) 125 mg daily which produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An increased dose of 175 mg daily produced excellent clinical response with no side effects. He developed [atrial fibrillation and flutter](#). [Digoxin](#) 0.25 mg daily was added to his therapy, and [desipramine](#) was discontinued. His [arrhythmia](#) was suppressed with the addition of [propafenone](#) 150 mg twice daily and 300 mg at bedtime. [Desipramine](#) 150 mg daily was again begun, at which point he experienced dry mouth, sedation, and shakiness; the [desipramine](#) serum level was measured at 2092 nmol/L. The [desipramine](#) was discontinued for five days, the side effects ceased, and [desipramine](#) therapy was resumed at 75 mg daily. The [desipramine](#) serum level was measured at 1130 nmol/L [466].

3.5.1.ML] [Propofol](#)

- 1)) Interaction Effect: additive cardiorespiratory effects
- 2)) Summary: Concomitant use of fospropofol and a benzodiazepine may result in additive cardiorespiratory effects due to the sedative action of both drugs[100]. Monitoring the patient for adverse effects may be warranted and possible dose adjustments may be necessary.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when fospropofol and a benzodiazepine are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7)) Probable Mechanism: CNS depression

3.5.1.MM] [Propoxyphene](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: probable
- 6)) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7)) Probable Mechanism: additive CNS depression
- 8)) Literature Reports

a)) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.MN] Propoxyphene

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[236], and [propoxyphene](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [propoxyphene](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, and diarrhea), and mental status changes (eg, 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 [240].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [propoxyphene](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.MO] Propranolol

- 1) Interaction Effect: increased [propranolol](#) exposure; increased risk of postural hypotension
- 2) Summary: Coadministration of [amitriptyline](#) (a CYP2D6 inhibitor) and [propranolol](#) (a CYP2D6 substrate) may result in increased [propranolol](#) exposure. Coadministration may also result in exacerbation of amitriptyline-induced hypotension. If coadministration is required, monitor patients for bradycardia and hypotension[973].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [amitriptyline](#) (a CYP2D6 inhibitor) and [propranolol](#) (a CYP2D6 substrate) should be undertaken with caution as this may result in increased [propranolol](#) exposure. Coadministration may also result in exacerbation of amitriptyline-induced hypotension. If coadministration is required, monitor patients for bradycardia and hypotension[973].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [propranolol](#) metabolism by [amitriptyline](#); exacerbation of amitriptyline-induced hypotension by [propranolol](#)

3.5.1.MP] Propyphenazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding.

including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.MQ] Proquazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.MR] Protriptyline

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

2) Summary: Concomitant use of [amitriptyline](#) and [protriptyline](#) is not common clinical practice. However if using [amitriptyline](#) and [protriptyline](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [amitriptyline](#) and [protriptyline](#) is not common clinical practice. However if using [amitriptyline](#) and [protriptyline](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.MS] 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[720].
- 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[720].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.MT] Quinestrol

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[854], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [855]. The effects of the interaction appear to be estrogen dose-related [856] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [857].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
- 8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 mg daily) and placebo, five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (50 mcg daily), while five patients received [imipramine](#) (150 mg daily) and [ethinyl estradiol](#) (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after two weeks, the five patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received [imipramine](#) 150 mg and [ethinyl estradiol](#) 50 mcg daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [845].

b)) A case reported by [846] demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 mg and [imipramine](#) 100 mg. The patient developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side-effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [847].

c)) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [848].

d)) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 mg at bedtime while 19 took [clomipramine](#) 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [849].

e)) Three patients who received [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 mg daily for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 mg daily for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 mg was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 mg daily who was prescribed [amitriptyline](#) 50 mg daily for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 mg daily and [amitriptyline](#) 50 mg daily. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [850].

f)) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 mcg or less of [ethinyl estradiol](#)) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [851].

g)) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [852]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [853].

3.5.1.MU] [Quinidine](#)

1)) Interaction Effect: increased [amitriptyline](#) plasma concentrations; an increased risk of [cardiotoxicity](#)

2J) Summary: Concomitant use of [amitriptyline](#), a CYP2D6 substrate, and [quinidine](#), a CYP2D6 inhibitor, may result in increased [amitriptyline](#) exposure and an increased risk of [amitriptyline](#) adverse effects due to inhibition of [amitriptyline](#) metabolism[773][987]. Additionally, the incidence of [cardiotoxicity](#) may also be increased if tricyclic antidepressants are coadministered with class IA antiarrhythmics due to similar cardiac effects of these drugs [232][233]. Therefore, an alternative treatment may be warranted. If [amitriptyline](#) and [quinidine](#) are coadministered, an [amitriptyline](#) dose adjustment should be considered [987]. Monitoring [amitriptyline](#) adverse effects during concomitant use should also be considered. If [quinidine](#) is discontinued, it may be necessary to increase the [amitriptyline](#) dose [773]. The patient may also need to be monitored for signs and symptoms of [cardiac toxicity](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [amitriptyline](#) and [quinidine](#) may result in increased [amitriptyline](#) exposure[773][987]. Additionally, the incidence of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) may also be increased if tricyclic antidepressants are coadministered with class IA antiarrhythmics due to similar cardiac effects of these drugs [232][233]. Therefore, consider an alternative treatment. If [amitriptyline](#) and [quinidine](#) are coadministered, consider an [amitriptyline](#) dose reduction [987]. Monitor for increased [amitriptyline](#) side effects if [amitriptyline](#) is coadministered with [quinidine](#). If [quinidine](#) is discontinued from therapy, an increased dose of [amitriptyline](#) may be required [773]. Also monitor the patient for signs and symptoms of [cardiac toxicity](#), including any changes in the ECG.

7J) Probable Mechanism: inhibition of CYP2D6-mediated [amitriptyline](#) metabolism by [quinidine](#); additive cardiac effects

8J) Literature Reports

aJ) An increased incidence in sudden death was observed in 6 out of 53 patients with cardiac disease receiving [amitriptyline](#), compared with 0 out of 53 in the control group. It was recommended that [amitriptyline](#) be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful [26]. Additional studies were conducted which further confirmed that [amitriptyline](#) was associated with an increased incidence of sudden death in patients with preexisting cardiac disease [430][431].

3.5.1.MV] [Quinine](#)

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

2J) Summary: Avoid using [amitriptyline](#) and [quinine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[352].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid using [amitriptyline](#) and [quinine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[352].

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

3.5.1.MW] [Ranolazine](#)

1J) Interaction Effect: increased tricyclic antidepressant plasma concentrations

2J) Summary: Coadministration of a tricyclic antidepressant and [ranolazine](#) may result in increased plasma concentrations of the antidepressant. As this may result in antidepressive adverse effects, caution is advised if a tricyclic antidepressant and [ranolazine](#) are used concomitantly. Monitoring of patients for increased side effects is recommended and a antidepressant dose reduction may be needed[414].

- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of [ranolazine](#) and CYP2D6 substrates, such as tricyclic antidepressants, may increase antidepressant plasma levels. When concurrent use of a tricyclic antidepressant and [ranolazine](#) is required, an antidepressant dose adjustment based on clinical response may be necessary[414].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated tricyclic antidepressant metabolism

3.5.1.MX] [Rasagiline](#)

- 1) Interaction Effect: severe CNS toxicity
- 2) Summary: Concomitant use of [rasagiline](#) and tricyclic antidepressants should be avoided. Concurrent administration or overlapping therapy with tricyclic antidepressants and nonselective MAOIs has been reported to cause serious, sometimes fatal, reactions; the mechanisms of these reactions are not fully understood. Signs and symptoms include severe CNS toxicity (behavioral and mental status changes, diaphoresis, muscular rigidity, [hypertension](#), and syncope) associated with [hyperpyrexia](#) and death. Data from clinical studies in which rasagiline-treated patients (n=115) were concomitantly exposed to tricyclic antidepressants are insufficient to rule out an interaction. At least 14 days should elapse after discontinuing [rasagiline](#) before initiating therapy with a tricyclic antidepressant[623].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [rasagiline](#) and a tricyclic antidepressant is not recommended. Wait at least 14 days after discontinuing [rasagiline](#) before initiating therapy with a tricyclic antidepressant[623].
- 7) Probable Mechanism: unknown

3.5.1.MY] [Remifentanyl](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

- a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.MZ| Rifapentine

- 1) Interaction Effect: decreased [amitriptyline](#) efficacy
- 2) Summary: [Rifapentine](#) is known to induce hepatic cytochrome P450 enzymes involved in the metabolism of [amitriptyline](#). When [rifapentine](#) and [amitriptyline](#) are administered together it may be necessary to increase the dose of [amitriptyline](#)[278].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients for reduced [amitriptyline](#) plasma concentrations and reduced [amitriptyline](#) efficacy. [Amitriptyline](#) doses may need to be increased when [rifapentine](#) is given concomitantly with [amitriptyline](#).
- 7) Probable Mechanism: induction by [rifapentine](#) of cytochrome P450 3A4 and P450 2C9 [amitriptyline](#) metabolism

3.5.1.NA| Risperidone

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Several antipsychotic agents are associated with QT-interval prolongation[282][283][284][285][286]. Although no formal drug interaction studies have been done, coadministration of a tricyclic antidepressant with an antipsychotic is not recommended [287].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [281].

3.5.1.NB| Ritonavir

- 1) Interaction Effect: increased [amitriptyline](#) serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: Coadministered [ritonavir](#) may increase serum concentrations of [amitriptyline](#), resulting in [amitriptyline](#) toxicity[320]. Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with [ritonavir](#) [321].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients for signs and symptoms of tricyclic antidepressant toxicity (anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#)). Reduce doses of [amitriptyline](#) as required.

7J) Probable Mechanism: decreased [amitriptyline](#) metabolism

3.5.1.NC] [Rizatriptan](#)

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

2J) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor, and [rizatriptan](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#)[444][236]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [rizatriptan](#) 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 [240].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [rizatriptan](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[444][236]. If coadministration is required, appropriate monitoring may be warranted.

7J) Probable Mechanism: additive serotonergic effect

3.5.1.ND] [Rofecoxib](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.NE] S-Adenosylmethionine

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: A single case has been reported of [serotonin syndrome](#) likely resulting from the combination of S-adenosylmethionine (S-AMe) and [clomipramine](#) [787]. S-AMe was shown to hasten the onset of therapeutic response of [imipramine](#) in a clinical trial involving 40 patients, without serotonergic side effects [788]. If therapy is initiated with S-AMe and a tricyclic antidepressant, the patient should be monitored closely for early signs of [serotonin syndrome](#). [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result [789].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: S-adenosylmethionine (S-AMe) used concomitantly with [imipramine](#) was found to decrease depressive symptoms sooner than [imipramine](#) alone (Berlanga et al, 1992). One case has been reported of [serotonin syndrome](#) likely resulting from concomitant use of S-AMe and [clomipramine](#) (Iruela et al, 1993). If S-AMe and a tricyclic antidepressant are used together, use low doses of each and titrate upward slowly, while monitoring closely for early signs of [serotonin syndrome](#) such as increasing anxiety, confusion, and disorientation.
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
- 8) Literature Reports

a) A 71 year-old female was hospitalized with anxiety, agitation, confusion, and symptoms of [serotonin syndrome](#). She had been taking S-adenosylmethionine 100 milligrams (mg) intramuscularly daily and [clomipramine](#) 25 mg daily for 10 days, which was then increased to 75 mg/day. Within 48-72 hours of the increased [clomipramine](#) dosage, she became progressively anxious, agitated, and confused. On admission she was verbally unresponsive and stuporous, with heart rate 130 beats/minute, respiratory rate 30 breaths/minute, temperature 40.5 degrees Celsius, diarrhea, myoclonus, generalized tremors, rigidity, hyperreflexia, shivering, diaphoresis, and dehydration. Temperature increased to 43 degrees Celsius during her hospital stay, with no documented infection. White blood cell count (WBC) was 13,040 mm³, lactic dehydrogenase was 662 units/liter (U/L), creatine phosphokinase was 8920 U/L, serum potassium 2.7 milliequivalents/liter (mEq/L), [creatinine](#) 1.1 mg/100 milliliter (mL) (laboratory reference values were not provided). A cranial [computed tomography](#) (CT) scan was normal. The patient was not taking neuroleptics. Serum benzodiazepine and tricyclic antidepressant levels were normal. Symptoms resolved gradually with 4 days of hydration and supportive care. The interaction was proposed to be a result of synergistic activity of S-adenosylmethionine and [clomipramine](#) [786].

3.5.1.NF] Sildenafil

- 1) Interaction Effect: Risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of serotonergic agents with sildenafil (a MAOI-type B) is contraindicated due to the potential for [serotonin syndrome](#). Use of serotonergic agents within 14 days of discontinuing a MAOI is also contraindicated [377].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of serotonergic agents with sildenafil (a MAOI-type B) is contraindicated due to the potential for [serotonin syndrome](#). Use of serotonergic agents within 14 days of discontinuing a MAOI is also contraindicated [377].

7J) Probable Mechanism: Additive serotonergic effects

3.5.1.NG| Salicylic Acid

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.NH| Salmeterol

1J) Interaction Effect: an increased risk of cardiovascular excitation

2J) Summary: Salmeterol should be administered with extreme caution to patients who are being treated with a tricyclic antidepressant, or within two weeks of the discontinuation of a tricyclic antidepressant[250]. Clinically significant changes in systolic and diastolic blood pressure, pulse rate, and [electrocardiograms](#) have been seen with the use of salmeterol, and these changes may be exacerbated by the use of a tricyclic antidepressant.

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: Close observation for adverse cardiovascular effects is warranted when these agents are administered concurrently or if salmeterol is given within two weeks of discontinuation of a tricyclic antidepressant.

7J) Probable Mechanism: potentiation of vascular effects

3.5.1.NI| Salsalate

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.NJ] [Saquinavir](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Both ritonavir-boosted [saquinavir](#) and this drug prolong the QT interval. The concomitant use of ritonavir-boosted [saquinavir](#) is contraindicated with drugs that are CYP3A4 substrates that can have life-threatening reactions with increased plasma levels, drugs that cause QT-interval prolongation, and with drugs that both increase [saquinavir](#) plasma concentrations and cause QT-interval prolongation. If concurrent use of ritonavir-boosted [saquinavir](#) and a QT-prolonging drug is required, perform a baseline ECG. Do not initiate coadministration if QT interval exceeds 450 msec. Perform an on-treatment ECG after 3 to 4 days of concurrent use; if the QT interval exceeds 480 msec or has increased more than 20 msec from baseline, discontinue one or both therapies[897].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Both ritonavir-boosted [saquinavir](#) and this drug prolong the QT interval. The concomitant use of ritonavir-boosted [saquinavir](#) is contraindicated with drugs that are CYP3A4 substrates that can have life-threatening reactions with increased plasma levels, drugs that cause QT-interval prolongation, and with drugs that both increase [saquinavir](#) plasma concentrations and cause QT-interval prolongation. If concurrent use of ritonavir-boosted [saquinavir](#) and a QT-prolonging drug is required, perform a baseline ECG. Do not initiate coadministration if QT interval exceeds 450 msec. Perform an on-treatment ECG after 3 to 4 days of concurrent use; if the QT interval exceeds 480 msec or has increased more than 20 msec from baseline, discontinue one or both therapies[897].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.NK] [Secobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[142][143][144][145][146].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a)) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [133][134][135][136][137].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [138]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [139]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [140]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [141].

3.5.1.NL] [Secobarbital](#)

1)) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2)) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.

3)) Severity: minor

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7)) Probable Mechanism: increased tricyclic antidepressant metabolism

8)) Literature Reports

a)) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.NM] [Selegiline](#)

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

2)) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[808][809][810][811]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), [myoclonus](#), and changes in mental status

[812]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [813]. A minimum of 14 days should elapse after discontinuing [selegiline](#) before initiating therapy with [amitriptyline](#) or a minimum of 7 days should elapse after discontinuing [amitriptyline](#) before initiating therapy with [selegiline](#) [814].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: The concurrent use of [amitriptyline](#) and [selegiline](#) is contraindicated. A minimum of 14 days should elapse after [selegiline](#) is discontinued before [amitriptyline](#) is initiated or allow a minimum of 7 days to elapse between the discontinuation of the [amitriptyline](#) and the initiation of therapy with [selegiline](#). Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [790][791][792][793][794][795]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [796].

b) The development of [serotonin syndrome](#) was reported due to administration of a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [797].

c) A drug interaction was reported when a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [798].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [799].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs

and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [800].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranlycypromine](#) in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexial state led to [disseminated intravascular coagulation](#) and eventual death [801].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranlycypromine](#) in any combination, and d) close monitoring of patients [802][792][793][803][804]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [805]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added [591]. Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [805]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [806][793][807].

3.5.1.NN] Sematilide

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

2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[330], [amiodarone](#) [331], azimilide [332], [bretylum](#) [333], [ibutilide](#) [334], sematilide [335], [dofetilide](#) [336], and [sotalol](#) [337]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [338][339].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [328].

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised [329].

3.5.1.NO] Sertindole

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

2) Summary: Several antipsychotic agents are associated with QT-interval prolongation[282][283][284][285][286]. Although no formal drug interaction studies have been done, coadministration of a tricyclic antidepressant with an antipsychotic is not recommended [287].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [281].

3.5.1.NP] [Sertraline](#)

1) Interaction Effect: increased exposure of CYP2D6 substrate and risk of [serotonin syndrome](#)

2) Summary: Caution is advised with concomitant administration of [sertraline](#) and drugs that are CYP2D6 substrates and serotonergic agents. [Sertraline](#) is a CYP2D6 inhibitor and has been associated with [serotonin syndrome](#) during monotherapy. Risk of this event is increased when [sertraline](#) is coadministered with other serotonergic agents. If coadministration is necessary, monitor for symptoms of [serotonin syndrome](#), especially with treatment initiation and dose increases. If [serotonin syndrome](#) is suspected, immediately discontinue [sertraline](#) and other serotonergic agents and provide supportive treatment[948].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [sertraline](#) and drugs that are CYP2D6 substrates and serotonergic agents. [Sertraline](#) is a CYP2D6 inhibitor and has been associated with [serotonin syndrome](#) during monotherapy. Risk of this event is increased when [sertraline](#) is coadministered with other serotonergic agents. If coadministration is necessary, monitor for symptoms of [serotonin syndrome](#), especially with treatment initiation and dose increases. If [serotonin syndrome](#) is suspected, immediately discontinue [sertraline](#) and other serotonergic agents and provide supportive treatment[948].

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

3.5.1.NQ] [Sevoflurane](#)

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

2) Summary: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#)[640].

3) Severity: major

4) Onset: unspecified

5) 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](#)[640].

7J) Probable Mechanism: additive effects on QT interval

3.5.1.NR] [Sibutramine](#)

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

2J) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[441], and [sibutramine](#), a serotonin, [norepinephrine](#), and [dopamine](#) reuptake inhibitor [441], affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#) [441][236]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [sibutramine](#) 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 [240].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [sibutramine](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[441][236]. If coadministration is required, appropriate monitoring may be warranted.

7J) Probable Mechanism: additive serotonergic effect

3.5.1.NS] [Skullcap](#)

1J) Interaction Effect: increased central nervous system depression

2J) Summary: In vitro studies demonstrate that several constituents of skullcap have affinity for the benzodiazepine binding site of the GABA-A receptor, and appear to compete with benzodiazepines for the site[210][211]. Theoretically, skullcap may have additive effects when administered with a benzodiazepine, yet if the binding is competitive in nature, skullcap may displace the benzodiazepine from the receptor and reduce its effectiveness. Caution is advised with concomitant use of skullcap and benzodiazepines until this potential interaction is better characterized.

3J) Severity: minor

4J) Onset: rapid

5J) Substantiation: theoretical

6J) Clinical Management: Monitor patients for increased central nervous system depression, and for altered effectiveness of benzodiazepine therapy.

7J) Probable Mechanism: several constituents of skullcap have demonstrated binding affinity for the benzodiazepine site of the GABA-A receptor

8J) Literature Reports

aJ) Constituents isolated from the organic solvent extract of skullcap root demonstrated binding affinity for the benzodiazepine (BZD) site of the GABA-A receptor. Wogonin and baicalein had the strongest affinity, scutellarein had moderate activity, and baicalin had weakest activity. All of these constituents contain the flavonoid phenylbenzopyrone nucleus, which binds to the benzodiazepine site. The concentrations at which 50 percent inhibition (IC₅₀) of

(3H)flunitrazepam binding occurred were as follows, wogonin 3.62 micromolar (mcM); baicalein 10.11 mcM; scutellarein 20.96 mcM; and baicalin 137.07 mcM, whereas the IC₅₀ of [diazepam](#) was 0.029 mcM [208].

b)) Constituents isolated from the water extract of skullcap root demonstrated activity on the [dopamine](#) D1, D2, 5-hydroxytryptamine, and benzodiazepine (BDZ) binding sites of gamma-amino butyric acid ([GABA](#)) receptors, but not on muscarinic [acetylcholine](#) M1, 5-HT₂ receptors or the [GABA](#) binding site of [GABA](#) receptors in vitro. Baicalein, oroxylin A and wogonin, flavone constituents of skullcap, showed weak binding to the BDZ sites while skullcapflavone II demonstrated binding comparable to that of [chlordiazepoxide](#) but 100-fold less than [flurazepam](#) [209].

3.5.1.NT] [Sodium Oxybate](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: In trials involving [sodium oxybate](#), [respiratory depression](#) was reported[101]. When used in combination with benzodiazepines, these drugs may have additive CNS and respiratory depressant effects.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7)) Probable Mechanism: CNS depression

3.5.1.NU] [Sodium Phosphate](#)

- 1)) Interaction Effect: an increased risk of QT interval prolongation
- 2)) Summary: Use caution when using [amitriptyline](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[354] [236]. Prolongation of QT interval, associated with [electrolyte imbalances](#) (eg, hypokalemia and [hypocalcemia](#)), and rare, but serious reports of [arrhythmias](#) have been noted with [sodium phosphate](#) therapy [354]. If concurrent therapy is required, monitor closely for QT prolongation.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution when using [amitriptyline](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[354] [236]. If concurrent therapy is required, monitor closely for QT prolongation.
- 7)) Probable Mechanism: additive effects on the QT interval

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

- 1)) Interaction Effect: an increased risk of QT interval prolongation
- 2)) Summary: Use caution when using [amitriptyline](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[354] [236]. Prolongation of QT interval, associated with [electrolyte imbalances](#) (eg, hypokalemia and [hypocalcemia](#)), and rare, but serious reports of [arrhythmias](#) have been noted with [sodium phosphate](#) therapy [354]. If concurrent therapy is required, monitor closely for QT prolongation.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical

6) Clinical Management: Use caution when using [amitriptyline](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[354] [236]. If concurrent therapy is required, monitor closely for QT prolongation.

7) Probable Mechanism: additive effects on the QT interval

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

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

2) Summary: Use caution when using [amitriptyline](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[354] [236]. Prolongation of QT interval, associated with [electrolyte imbalances](#) (eg, hypokalemia and [hypocalcemia](#)), and rare, but serious reports of [arrhythmias](#) have been noted with [sodium phosphate](#) therapy [354]. If concurrent therapy is required, monitor closely for QT prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when using [amitriptyline](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[354] [236]. If concurrent therapy is required, monitor closely for QT prolongation.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.NX] [Sodium Salicylate](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.NY] [Solifenacin](#)

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

2) Summary: The concomitant use of [solifenacin](#) with other drugs that prolong the QT interval, such as [amitriptyline](#), should be approached with caution as coadministration may result in additive effects on

QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#)[302]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the concomitant use of [solifenacin](#) with other drugs that prolong the QT interval, such as [amitriptyline](#), as coadministration may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#)[302]. If concomitant use is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.NZ| [Sorafenib](#)

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

2) Summary: Use caution when using [amitriptyline](#) and [sorafenib](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concomitant therapy is required, monitor for prolonged QT intervals[353].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when using [amitriptyline](#) and [sorafenib](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concomitant therapy is required, monitor for prolonged QT intervals[353].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.OA| [Sotalol](#)

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

2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[330], [amiodarone](#) [331], azimilide [332], [bretylium](#) [333], [ibutilide](#) [334], sematilide [335], [dofetilide](#) [336], and [sotalol](#) [337]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [338][339].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [328].

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetry monitoring is advised [329].

3.5.1.OB| 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](#)[898].
- 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](#)[898].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.OC| Spiramycin

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) and spiramycin have been shown to prolong the QTc interval at the recommended therapeutic dose[951][952]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as spiramycin, is not recommended [953].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of spiramycin and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.OD| St John's Wort

- 1) Interaction Effect: reduced benzodiazepine effectiveness
- 2) Summary: Concomitant use of [alprazolam](#), [midazolam](#), or [quazepam](#) (all CYP3A4 substrates) with St. John's wort (CYP3A4 inducer) was shown to induce benzodiazepine metabolism in trials of healthy participants[119][120][121][122]. St. John's wort did not, however, significantly affect [quazepam](#) efficacy [119]. Because other benzodiazepines are also CYP3A4 substrates, similar results can be expected when another benzodiazepine is coadministered with St. John's wort. Monitoring benzodiazepine plasma concentrations and efficacy may be warranted if used concomitantly with St. John's wort. If a patient is taking St. John's wort at the time of surgery during which [midazolam](#) or any other benzodiazepine is to be used for sedation, it may be necessary to monitor the patient for signs of decreased benzodiazepine efficacy and adjust the benzodiazepine dose when needed.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: established
- 6) Clinical Management: Concomitant use of [alprazolam](#), [midazolam](#), or [quazepam](#) with St. John's wort was shown to induce the CYP3A4-mediated metabolism of the benzodiazepine in studies of healthy participants[119][120][121][122]. Because benzodiazepines are metabolized by CYP3A4 pathways, similar results would be expected if any benzodiazepine was coadministered with St. John's wort. Therefore, consider monitoring for alterations in the therapeutic and adverse effects of the benzodiazepine if used concomitantly with St. John's wort. If a patient is taking St. John's wort at the time of surgery during which

[midazolam](#) or any other benzodiazepine is to be used for sedation, consider monitoring the patient closely for signs of reduced benzodiazepine effectiveness and adjusting the benzodiazepine dose, if necessary.

7j) Probable Mechanism: induction of CYP3A4-mediated metabolism of the benzodiazepine by St. John's wort

8j) Literature Reports

a) Concomitant use of [quazepam](#) and St. John's wort decreased [quazepam](#) plasma concentrations, but did not affect [quazepam](#) efficacy, in a randomized, double-blind, placebo-controlled, crossover study of 13 healthy adult males. Participants refrained from grapefruit-containing products and herbal supplements or tea; caffeine-containing products were withheld. Participants received either oral St. John's wort (standardized to 0.3% hypericin) 300 mg 3 times/day or placebo for 14 days. On day 14, a single [quazepam](#) 15-mg oral dose was given. Blood samples were obtained just prior to and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hrs after the [quazepam](#) dose. At 48 hrs, [quazepam](#) C_{max} and AUC were reduced by 8.7 nanograms (ng)/mL (95% confidence interval (CI), -17.1 to -0.2 ng/mL; p less than 0.05) and by 55 ng hr/mL (95% CI, -96 to -15 ng hr/mL; p less than 0.05), respectively, in the St. John's wort group compared with the placebo group. [Quazepam](#) T_{max} and t(1/2) and 2-oxoquazepam C_{max}, AUC, T_{max}, and t(1/2) were not significantly affected by St. John's wort. The 2-oxoquazepam to [quazepam](#) ratio in the C_{max} was higher in the St. John's wort group compared with the placebo group (0.47 vs 0.4 ng/mL; p less than 0.01). The urinary ratio of 6-beta-hydroxycortisol to cortisol was increased with St. John's wort compared with placebo (ratio, 2.1; 95% CI, 0.85 to 3.4; p less than 0.05); an increased urinary ratio of cortisol metabolite to cortisol is indicative of hepatic CYP3A4 activity. [Quazepam](#) efficacy was not significantly changed with the coadministration of St. John's wort as reflected in the visual analogue scale (VAS), which evaluates self-ratings of sedative-like effects, and the digit symbol substitution test (DSST) which measures psychomotor performance [119].

b) St. John's wort significantly reduced the bioavailability of [midazolam](#) by 50% after 12 days in an open-label, crossover study of 22 healthy subjects. Subjects received St. John's wort (Jarsin 300, LI 160, Lichtwer Pharma) 300 mg three times daily for 12 days followed by a single dose of [midazolam](#) 4 mg orally or 1 mg intravenously. Oral clearance of [midazolam](#) was increased by 168%, and maximum concentration was reduced by 53% (both p less than 0.0001) [120].

c) St. John's wort significantly induced the metabolism of [midazolam](#) after 4 weeks in a randomized, open-label trial of 12 healthy subjects. Subjects received St. John's wort (*Hypericum perforatum*, standardized to 0.3% hypericin) 300 mg orally three times daily for 28 days. The St. John's wort was from a single lot but was not tested to verify label claims. Subjects received oral [midazolam](#) 8 mg prior to supplementation and on day 27. St. John's wort increased the mean 1-hour 1-hydroxymidazolam/[midazolam](#) ratio by 98% (p less than 0.0001), indicating induction of CYP3A4. Female subjects experienced a 74% greater increase than males (p = 0.029). In males, the rate of metabolism correlated with body mass index [123].

d) St. John's wort reduced the bioavailability of oral [midazolam](#) by 50% after 14 days in an open-label study of 12 healthy subjects, while single dose St. John's wort had no effect. In the short-term study, subjects took St. John's wort (Sundown Herbals, Boca Raton, FL) 300 mg one hour prior to a single dose of intravenous [midazolam](#) 0.05 mg/kg. Oral [midazolam](#) syrup 5 mg was administered 24 hours after St. John's wort. In the long-term study, subjects took St. John's wort 300 mg three times daily for 14 to 15 days followed by the same [midazolam](#) doses. St. John's wort was from a single lot and was labeled to contain 900 mcg hypericin. Ten randomly selected capsules tested contained 840 +/- 56 mcg hypericin and 11 +/- 0.63 mg hyperforin. Following 14 days of St. John's wort use, AUC and C_{max} of oral [midazolam](#) were reduced by 50%, and oral clearance increased

2-fold (all p less than 0.05). AUC of intravenous [midazolam](#) was nonsignificantly reduced by 21%. These results suggest that St. John's wort increased first-pass elimination of [midazolam](#) with reduced availability likely due to CYP3A4 induction at the gut wall [121].

e) St. John's wort significantly increased the plasma clearance of [alprazolam](#), (studied as a CYP3A4 probe drug). In an open-label, crossover study, healthy adult subjects ($n=12$) received a single, oral dose of St. John's wort 300 mg (standardized to 0.12% to 0.3% hypericin (LI 160, Kira(R))) 3 times daily for 14 days, followed by another single dose of oral [alprazolam](#) 2 mg. Compared with baseline, St. John's wort induced a 2-fold increase in plasma clearance of [alprazolam](#) (p less than 0.001) and a 2-fold decrease in AUC for [alprazolam](#) (p less than 0.001). [Alprazolam](#) elimination half-life was also reduced (from 12.4 to 6 hours; p less than 0.001) [122].

3.5.1.OE] St John's Wort

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

2) Summary: Coadministration of [amitriptyline](#) and St. John's Wort decreased the area under the concentration-time curve of [amitriptyline](#) and its metabolite [nortriptyline](#)[613]. Theoretically, since St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity [614][615], [serotonin syndrome](#) could result when St. John's Wort is taken along with a tricyclic antidepressant such as [amitriptyline](#). This theoretical risk of [serotonin syndrome](#) is also based on case reports of [serotonin syndrome](#) resulting from concomitant use of selective serotonin reuptake inhibitors with tricyclic antidepressants [616], as well as concomitant use of monoamine oxidase inhibitors with tricyclic antidepressants [617][618][619]. The risk of [serotonin syndrome](#) is decreased if [amitriptyline](#) levels are reduced by St. John's Wort. To maintain maximal effectiveness of [amitriptyline](#) as well as to avoid any potential risk of [serotonin syndrome](#), avoid concomitant use of St. John's Wort and [amitriptyline](#).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Avoid concomitant use of St. John's Wort with [amitriptyline](#).

7) Probable Mechanism: induction of metabolizing enzymes; additive serotonergic effect

8) Literature Reports

a) In an open-label study involving twelve depressed patients, the effect of St. John's Wort on the steady-state pharmacokinetics of [amitriptyline](#), a tricyclic antidepressant, was investigated. St. John's Wort (900 mg/day) was administered concomitantly with [amitriptyline](#) (75 mg twice daily) for a minimum of fourteen days. A 21.7% decrease (p equal to 0.034) in area under the concentration-time curve (AUC) of [amitriptyline](#) and a 41.6% decrease (p equal to 0.002) in the AUC of [nortriptyline](#), the metabolite of [amitriptyline](#) occurred. The cause of the interaction may be attributed to the induction of drug metabolizing enzymes or drug transporters by St. John's Wort [612].

3.5.1.OF] [Sufentanil](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: Concomitant use of opioid pain or [cough](#) medicines and benzodiazepines may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Reserve concomitant use of opioid analgesics with benzodiazepines to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response[126]. Limit the duration of concomitant use [127]. Monitor for [respiratory depression](#) and sedation. Avoid concomitant use of prescription opioid [cough](#) medications with CNS depressants [126].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every 6 hours) and [alprazolam](#) (1 mg) therapy increased the half-life of [alprazolam](#) by greater than 50% (11 vs 18 hours), which may lead to excessive CNS depression [128].

3.5.1.OG| [Sulfamethoxazole](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) and cotrimoxazole have been shown to prolong the QTc interval at the recommended therapeutic dose[781][782]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as cotrimoxazole, is not recommended [783].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.OH| [Sulindac](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.OI] 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[611].
- 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[611].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.OJ] Sultopride

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Several antipsychotic agents are associated with QT-interval prolongation[282][283][284][285][286]. Although no formal drug interaction studies have been done, coadministration of a tricyclic antidepressant with an antipsychotic is not recommended [287].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [281].

3.5.1.OK] Sumatriptan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of [sumatriptan](#) and tricyclic antidepressants may increase the risk for [serotonin syndrome](#). Symptoms may occur within minutes to hours of administration of an initial or increased dose of the serotonergic agent. [Sumatriptan](#) should be discontinued if [serotonin syndrome](#) is suspected[981][982][983].
- 3) Severity: major

- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sumatriptan](#) and tricyclic antidepressants may increase the risk for [serotonin syndrome](#). Symptoms may occur within minutes to hours of administration of an initial or increased dose of the serotonergic agent. Discontinue [sumatriptan](#) if [serotonin syndrome](#) is suspected[981][982][983].
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.OL] [Sunitinib](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [amitriptyline](#) and [sunitinib](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[340].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [amitriptyline](#) and [sunitinib](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[340].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.OM] [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[442][443].
- 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[442][443].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.ON] [Tan-Shen](#)

- 1) Interaction Effect: increased risk of central nervous system depression
- 2) Summary: Miltirone and the other nine diterpene quinones present in *Salvia miltiorrhiza* (Tan-shen) appear to act as partial agonists at central benzodiazepine receptors[194]. While this is likely responsible for anxiolytic activity of tan-shen, it appears that sedation, muscle relaxation, and addiction qualities are minimized [194]. Because tan-shen acts as a partial and not a full agonist, the clinical significance of the interaction is unknown. Caution is advised until the magnitude of the interaction is better understood.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised if tan-shen is used concomitantly with a benzodiazepine. Patients should be advised to avoid operating heavy machinery until the magnitude of the interaction is known.
- 7) Probable Mechanism: partial agonist activity at central benzodiazepine receptors

8) Literature Reports

a) Ten diterpene quinones present in the Chinese medicinal herb *Salvia miltiorrhiza* (tan-shen) have been shown to inhibit binding of (3H) flunitrazepam to central benzodiazepine receptors. These quinones, isolated from the ethereal extract of the roots of *Salvia miltiorrhiza*, exhibited IC50s ranging from 0.3 to 36.2 mcml (the IC50 is the drug concentration required to provide 50% inhibition of specific (3H) flunitrazepam binding). Miltirone had the highest potency (IC50=0.3 mcml) [193]. Oral administration of miltirone (10-60 mg/kg) increased the number of punished crossings of mice in the Four-Plate Test which is an indication of clinical tranquilizing effects. The magnitude of this effect was lower than that observed with [diazepam](#) [193].

3.5.1.OO| Tapentadol

1) Interaction Effect: an increase in CNS and [respiratory depression](#)

2) Summary: The concomitant use of tapentadol with other CNS depressants, including sedatives, may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[126].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of tapentadol with other CNS depressants, including sedatives, to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[126].

7) Probable Mechanism: additive CNS depression

3.5.1.OP| Tapentadol

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

2) Summary: Concurrent use of tapentadol and a tricyclic antidepressant may result in [serotonin syndrome](#), which may be life-threatening. Symptoms of [serotonin syndrome](#) may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea[647].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of tapentadol and a tricyclic antidepressant may result in a life-threatening condition called [serotonin syndrome](#). If these agents are used together, monitor the patient closely for symptoms of [serotonin syndrome](#) (restlessness, [hyperthermia](#), hyperreflexia, incoordination), especially during treatment initiation and dose increases[647].

7) Probable Mechanism: additive serotonergic effect

3.5.1.OQ| Tedisamil

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

2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[330], [amiodarone](#) [331], azimilide [332], [bretylum](#) [333],

[ibutilide](#) [334], [sematilide](#) [335], [dofetilide](#) [336], and [sotalol](#) [337]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [338][339].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [328].

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised [329].

3.5.1.OR] Teduglutide

1) Interaction Effect: increased exposure of orally administered benzodiazepines

2) Summary: Coadministration of teduglutide with an oral medication that requires titration, such as a benzodiazepine, may significantly increase absorption of the benzodiazepine. In clinical trials, a patient taking a benzodiazepine who was treated with concomitant teduglutide experienced altered mental status that progressed to coma. A reduced dose of oral drugs requiring titration (eg, benzodiazepines) may be necessary when administered concomitantly with teduglutide[161]. If coadministration is necessary, the patient should be monitored for increased benzodiazepine side effects.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if teduglutide is coadministered with an oral medication that requires titration, such as a benzodiazepine. Concomitant use may cause increased absorption of benzodiazepines and require dose adjustment of the orally administered benzodiazepine[161]. Monitor for increased benzodiazepine side effects if a patient is taking teduglutide concomitantly with an oral benzodiazepine.

7) Probable Mechanism: unknown

8) Literature Reports

a) In a placebo-controlled clinical trial of teduglutide in adults with [short bowel syndrome](#) who were dependent on parenteral nutrition support, 1 woman who received teduglutide 0.05 mg/kg/day with concomitant oral [prazepam](#) had a dramatic deterioration in mental status, progressing to coma during the first week of study treatment. The level of [prazepam](#) in her blood was more than 300 mcg/L upon being admitted to the ICU. The coma resolved 5 days after teduglutide and [prazepam](#) were discontinued [161].

3.5.1.OS] Telavancin

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

2) Summary: In clinical trials, prolongation of the QT interval was observed with telavancin use. Therefore, caution is advised if telavancin is used concomitantly with other drugs that may prolong the QT interval[1001], such as [amitriptyline](#). If concomitant therapy is required, closely monitor for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on QT interval prolongation, use caution if telavancin is administered concurrently with other drugs that may prolong the QT interval[1001], such as [amitriptyline](#). If concomitant therapy is required, closely monitor for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

8) Literature Reports

a) In 3 clinical trials, QTc prolongation greater than 60 msec was observed in 1.5% (15 of 2062) of patients treated with telavancin 10 mg/kg compared with 0.6% (6 of 2062) patients treated with [vancomycin](#). In these studies, 21% (214 of 1029) of telavancin-treated patients and 16% (164 of 1033) of vancomycin-treated patients received concomitant medications known to prolong QTc. Of the patients experiencing QTc prolongation of greater than 60 msec, 9 telavancin-treated patients and 1 vancomycin-treated patient received concomitant medications known to prolong the QTc interval, and less than 1% in each group did not receive a concomitant medication known to prolong the QTc interval. A separate analysis revealed that 1 telavancin-treated patient and 2 vancomycin-treated patients experienced a QTc greater than 500 msec. No patients experienced a cardiac adverse event attributed to QTc prolongation [1001].

b) In a randomized, double-blind, multiple-dose, positive- and placebo-controlled, parallel study, maximum QTc prolongation of 11.6 msec (upper 90% confidence limit (CL), 16 msec) and 15.1 msec (upper 90% CL, 20 msec) was observed in patients treated with telavancin 7.5 mg/kg and 15 mg/kg, respectively, compared with 21.6 msec (upper 90% CL 26 msec) in the positive-control group. Healthy subjects (n=160) were randomized to telavancin 7.5 mg/kg, telavancin 15 mg/kg, positive control, or placebo infused over 60 minutes once daily for 3 days. At the end of the infusion, the mean maximum baseline-corrected, placebo-corrected QTc prolongation estimate for telavancin 10 mg/kg (based on interpolation of the data from patients treated with telavancin 7.5 mg/kg and 15 mg/kg) was 12 to 15 msec compared with 22 msec for the positive control. One hour after infusion, the maximum QTc prolongation for telavancin-treated patients was 6 to 9 msec compared with 15 msec for the positive control [1001].

3.5.1.OT] [Telithromycin](#)

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

2) Summary: [Telithromycin](#) may prolong the QT interval in some patients[322]. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [telithromycin](#) and tricyclic antidepressants is not recommended [323].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of [telithromycin](#) and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.OU| Tenoxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.OV| Terbinafine

- 1) Interaction Effect: increased exposure of [amitriptyline](#)
- 2) Summary: Concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#). Poor metabolizers are especially at risk. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and adjust the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#), especially in poor metabolizers. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and reduce the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[236].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amitriptyline](#)

3.5.1.OW| Terfenadine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [terfenadine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[896].
- 3) Severity: contraindicated
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [terfenadine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[896].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.OX] Tetrabenazine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Avoid using [amitriptyline](#) and tetrabenazine concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[411].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid using [amitriptyline](#) and tetrabenazine concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[411].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.OY] Theophylline

- 1) Interaction Effect: decreased benzodiazepine effectiveness
- 2) Summary: [Theophylline](#) has been shown to reverse the sedative effects of benzodiazepines[111][112][113][114]. A larger dose of benzodiazepine may be needed to produce sedation in a theophylline-treated patient. [Respiratory depression](#) may occur if [theophylline](#) is discontinued without a reduction of the benzodiazepine dose [115].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor the patient for benzodiazepine clinical effectiveness. A larger than usual benzodiazepine dose may be required in a theophylline-treated patient. Benzodiazepine toxicity ([respiratory depression](#), sedation, dizziness, ataxia, weakness, decreased cognition or motor performance) may occur if [theophylline](#) is discontinued without a subsequent reduction in the benzodiazepine dose.
- 7) Probable Mechanism: [theophylline](#) blocks [adenosine](#) receptors
- 8) Literature Reports

a) Eight healthy male volunteers participated in a study which demonstrated the antagonistic properties of [theophylline](#) on diazepam-induced [psychomotor impairment](#). Subjects received an oral dose of [diazepam](#) 0.25 mg/kg, followed 40 minutes later by an intravenous infusion of 100 mL normal saline with or without [theophylline](#) 4.4 mg/kg. All subjects were tested twice: one time receiving [theophylline](#) and the other time receiving placebo. [Theophylline](#) reversed some of the diazepam-induced [psychomotor impairment](#) as measured by the digit symbol substitution test, card sorting, and three questionnaires which measured mood, anxiety, and distress. The antagonism caused by [theophylline](#) may be attributed to the stimulant action caused by methylxanthines on the central nervous system through [adenosine](#) receptor blockade [102].

b) Intravenous [theophylline](#) was reported to reverse the sedation produced by intravenous [diazepam](#) in patients undergoing [genitourinary surgery](#). Patients were given intravenous doses of [diazepam](#) during surgery to maintain deep sedation, followed by administration of intravenous [aminophylline](#) (60 to 120 mg) or normal saline postoperatively. Rapid [reversal of sedation](#) occurred in [aminophylline](#) patients as compared to no response in saline patients [103]. Other

studies and case reports have also shown that [theophylline](#) antagonizes the sedative effects of [diazepam](#) [104][105].

c) Three case reports described patients who had the sedative effects of [lorazepam](#) reversed postoperatively by the administration of [aminophylline](#) 1 mg/kg intravenously [106]. This same [aminophylline](#) dose was used to reverse the sedative effects of [midazolam](#) in three other patients [107]. [Theophylline](#) also was demonstrated to reverse the sedative and psychomotor properties of flunitrazepam in healthy volunteers [108].

d) Less successful rates have been reported when utilizing [aminophylline](#) to reverse benzodiazepine oversedation. Of the six patients reported, all of whom had received [midazolam](#), five patients showed no change in the level of consciousness after the administration of [aminophylline](#) 75 mg. One patient did experience quick and sudden awakening after [aminophylline](#) was given. The author suggests that there may be wide individual variations within the population to the effects of [aminophylline](#) antagonism on benzodiazepines [109].

e) To determine the mechanism by which [theophylline](#) antagonizes benzodiazepines, oral [alprazolam](#) 1 mg daily for seven days was administered to six patients who were receiving [theophylline](#) and to seven patients who were not receiving [theophylline](#) treatment. Serum [alprazolam](#) levels were significantly lower in patients on concurrent [theophylline](#) therapy, and the levels continued to decrease during each day of the study. In patients who were not receiving [theophylline](#), serum [alprazolam](#) levels were within the therapeutic range. The authors concluded that the antagonism of the anxiolytic effects of benzodiazepines by [theophylline](#) may be due to decreased serum benzodiazepine levels in these patients [110].

3.5.1.OZ] Thiopental

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects[142][143][144][145][146].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [133][134][135][136][137].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [138]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [139]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [140]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [141].

3.5.1.PA] Thiopental

- 1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
- 2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[888][889][890]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [891]. These drugs also have additive CNS and respiratory depressant effects.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
- 7) Probable Mechanism: increased tricyclic antidepressant metabolism
- 8) Literature Reports

a) The pharmacokinetics of a single oral dose of **desipramine** (100 mg) were studied in eight epileptic patients chronically treated with **phenobarbital** and in eight drug-free healthy controls [887]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma **desipramine** concentrations (74 nmol/L vs. 107 nmol/L), smaller **desipramine** area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter **desipramine** elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.PB] Thioridazine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of **thioridazine** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[622].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of **thioridazine** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[622].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.PC] Tiaprofenic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including **intracranial hemorrhage** within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.PD] Tibolone

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[315], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [316]. The effects of the interaction appear to be estrogen dose-related [317] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [318].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
- 8) Literature Reports

a) A study evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the

combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [306].

b)) A case reported by [307] demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side-effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [308].

c)) A study evaluated women who received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [309].

d)) A study evaluated the effects of oral contraceptives on [clomipramine](#) in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [310].

e)) Three patients who received [conjugated estrogens](#) and tricyclic antidepressants concurrently acquired [akathisia](#). A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [311].

f)) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [312].

g)) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [313]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [314].

3.5.1.PE] Tiotropium

- 1) Interaction Effect: increased risk of anticholinergic side effects
- 2) Summary: Treatment with both [tiotropium](#) and this drug may produce additive anticholinergic effects. Avoid concomitant use with other anticholinergic agents[440].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Treatment with both [tiotropium](#) and this drug may produce additive anticholinergic effects. Avoid concomitant use with other anticholinergic agents[440].
- 7) Probable Mechanism: additive anticholinergic effects

3.5.1.PF] Tolfenamic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.PG] Tolmetin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.PH] Toloxatone

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

2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[740][741][742][743]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [744]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [745].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [722][723][724][725][726][727]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [728].

b) [Serotonin syndrome](#) occurred in 2 patients administered a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [729].

c) A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months and subsequently switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were

described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [730].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [731].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [732].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranylcypromine](#) in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to [disseminated intravascular coagulation](#) and eventual death [733].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranylcypromine](#) in any combination, and d) close monitoring of patients [734][724][725][735][736]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [737]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [737]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [738][725][739].

3.5.1.PII] [Toremifene](#)

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

2) Summary: Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), the concomitant use of [amitriptyline](#) with [toremifene](#) should be avoided. If treatment with [amitriptyline](#) is warranted, interrupt [toremifene](#) therapy; however, if coadministration of [amitriptyline](#) with [toremifene](#) can not be avoided, monitor for QT prolongation. Consider [monitoring ECG](#) at baseline and during treatment as indicated in patients at increased risk of QT prolongation[538].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [toremifene](#) with [amitriptyline](#) may result in additive effects on the QT interval and should be avoided. If treatment with [amitriptyline](#) is required, interruption of [toremifene](#) is recommended; however, if concomitant use is necessary, closely monitor for QT prolongation. Consider [monitoring ECG](#) at baseline and during treatment as indicated in patients at increased risk of QT prolongation[538].

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

3.5.1.PJ] Tramadol

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

2J) Summary: The concomitant use of [tramadol](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[126].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of [tramadol](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[126].

7J) Probable Mechanism: additive CNS depression

3.5.1.PK] Tramadol

1J) Interaction Effect: an increased risk of seizures, [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes), opioid toxicity, and increased concentrations of [tramadol](#) and decreased concentrations of [tramadol](#) active metabolite, M1

2J) Summary: Concomitant use of [tramadol](#) and tricyclic antidepressants (TCAs), such as [amitriptyline](#) increases the risk for seizures and [serotonin syndrome](#), even if [tramadol](#) is used within the recommended dosage range. Additionally, concomitant use of [tramadol](#) (a CYP2D6 substrate) with CYP2D6 inhibitors (eg, [amitriptyline](#)) can inhibit metabolism of [tramadol](#) to the active metabolite, M1, potentially causing reduced analgesia. Furthermore, increased [tramadol](#) concentrations because of inhibition of CYP2D6-mediated metabolism may cause opioid toxicity. If concomitant use of [tramadol](#) with a serotonergic agent, including TCAs, is clinically warranted, caution is advised and careful observation of the patient is recommended, particularly during treatment initiation and dose increases[776]. Also, consider monitoring patients for signs and symptoms of opioid toxicity or decreased analgesic effect of [tramadol](#).

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: theoretical

6J) Clinical Management: Caution is advised with concomitant use of [amitriptyline](#) and [tramadol](#). Concomitant use of [tramadol](#) with a tricyclic antidepressant (TCA), such as [amitriptyline](#), increases the risk for seizures and [serotonin syndrome](#), even if [tramadol](#) is used within the recommended dosage range. Additionally, opioid toxicity and reduced analgesia may occur. If concomitant use of [tramadol](#) and a TCA is clinically warranted, careful observation is recommended, particularly during treatment initiation and dose increases[776]. Consider monitoring patients for signs and symptoms of opioid toxicity, as well as decreased analgesic effect of [tramadol](#).

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

3.5.1.PL] Tranylcypromine

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

2)) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#) [833][834][835][836]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [837]. The concurrent administration of [amitriptyline](#) and a MAOI is contraindicated [838].

3)) Severity: contraindicated

4)) Onset: delayed

5)) Substantiation: established

6)) Clinical Management: [Amitriptyline](#) is contraindicated with monoamine oxidase inhibitor (MAOI) therapy. If [amitriptyline](#) is replacing treatment with a MAOI, a minimum of 14 days should elapse after the MAOI is discontinued before [amitriptyline](#) is initiated. Low doses of [amitriptyline](#) should be employed and gradually titrated to optimum response.

7)) Probable Mechanism: altered catecholamine uptake and metabolism

8)) Literature Reports

a)) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [815][816][817][818][819][820]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [821].

b)) The development of [serotonin syndrome](#) was reported due to administration of a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [822].

c)) A drug interaction was reported when a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [823].

d)) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [824].

e)) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs

and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [825].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranlycypromine](#) in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexial state led to [disseminated intravascular coagulation](#) and eventual death [826].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranlycypromine](#) in any combination, and d) close monitoring of patients [827] [817][818][828][829]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [830]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added [591]. Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [830]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [831][818][832].

3.5.1.PM] [Trazodone](#)

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](#)[453]. 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 [240]. 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](#)[453]. 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.PN] [Trifluoperazine](#)

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

2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines[341][342][343]. Other phenothiazines may have similar effects, though no reports are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation [344]. Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic antidepressants were taken together, likely due to inhibition of their metabolism [345][346][347][348].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent administration of a phenothiazine and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive effect on QT interval

3.5.1.PO| Trimethoprim

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

2) Summary: Tricyclic antidepressants (TCAs) and cotrimoxazole have been shown to prolong the QTc interval at the recommended therapeutic dose[781][782]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as cotrimoxazole, is not recommended [783].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.PP| Trimipramine

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

2) Summary: Concomitant use of [amitriptyline](#) and [trimipramine](#) is not common clinical practice. However if using [amitriptyline](#) and [trimipramine](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [amitriptyline](#) and [trimipramine](#) is not common clinical practice. However if using [amitriptyline](#) and [trimipramine](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[236].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.PQ| 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[984][985][986]. 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[984][985][986].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.PR] Tryptophan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor, and tryptophan affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#)[236]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) 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 [240].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and tryptophan, as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.PS] [Valdecoxib](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and tricyclic antidepressants as this may cause an increased risk of bleeding, including [intracranial hemorrhage](#) within 30 days of concomitant use[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised if NSAIDs and tricyclic antidepressants are coadministered. Concomitant use of NSAIDs and tricyclic antidepressants may cause an increased risk of bleeding, including [intracranial hemorrhage](#)[436]. When NSAIDs and tricyclic antidepressants are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [436].

3.5.1.PT] Valerian

- 1)** Interaction Effect: additive CNS depression or reduced effectiveness of the benzodiazepine
- 2)** Summary: In one case report, valerian and passionflower used concurrently with [lorazepam](#) resulted in additive CNS depressive effects[162]. Valerian extracts have shown affinity for central and peripheral benzodiazepine receptors as well as barbiturate and GABA-A receptors [170][163]. Valerian extract displaced the benzodiazepine fluorodiazepam from the receptor [163]. The clinical effect may be additive or reduced effectiveness of benzodiazepines depending on the nature of the binding. It is recommended that patients be asked about herbal product use during intake of personal history [162]. Monitoring for altered effectiveness of the benzodiazepine should be considered with concurrent use.
- 3)** Severity: moderate
- 4)** Onset: rapid
- 5)** Substantiation: theoretical
- 6)** Clinical Management: Concomitant use of valerian and benzodiazepines may resulted in additive CNS depressive effects or may decreased the effectiveness of benzodiazepines. It is recommended that patients be asked about herbal product use during intake of personal history[162][163]. Monitor for altered effectiveness of the benzodiazepine during concurrent use.
- 7)** Probable Mechanism: additive effects on the benzodiazepine receptor, possible displacement of the benzodiazepine from its receptor
- 8)** Literature Reports

a) A case report describes a potentiated CNS depressive effect in a 40-year-old man following concomitant use of [lorazepam](#) with valerian and passionflower. The patient, who had been treating with [lorazepam](#) 2 mg/day for 2 months with no adverse effects, self-administered an infusion of valerian subterranean parts (estimated dose, 300 mg). 2 hours before going to bed for 2 consecutive days. On day 3, he instead ingested 3 oral tablets of dry extract from valerian rhizomes (300 mg/tablet) plus roots and aerial parts of passionflower (380 mg/tablet) at 1 hour intervals before bedtime. Nervousness and mild shaking dissipated after going to bed followed by extreme somnolence. After taking the same dose of the valerian root/passionflower product on day 4, he experienced more severe symptoms including substantial hand shaking, dizziness, and palpitations before bedtime followed by profound somnolence. Upon presentation after 32 hours of experiencing these CNS symptoms, he was observed to have nervousness while speaking and demonstrated anxious behavior without shaking. He had a history of general anxiety disorders and dream disorders. His family history was negative for essential tremor and there were no metabolic, [renal](#), or [hepatic disorders](#), [high blood pressure](#), or drug allergies. Because a drug interaction was suspected, the patient was continued on [lorazepam](#) but withdrawn from valerian and passionflower and symptoms resolved. It is postulated that the valerian root and passionflower have additive or synergistic effects on the inhibitory activity of benzodiazepines binding to the [gamma-aminobutyric acid \(GABA\)](#) receptors [162].

b) The amount of the amino acid [gamma-aminobutyric acid \(GABA\)](#) in aqueous and hydroalcoholic extracts of valerian is sufficient to explain its (3H)muscimol displacement effect at [GABA](#) receptor sites during in vitro tests. The [GABA](#) content of the aqueous extract is also sufficient to cause release of (3H)[GABA](#) in synaptosomes through homologous exchange, accounting for this in vitro effect as well. Since [GABA](#) cannot effectively cross the blood-brain barrier when given in the amounts available in the extracts, it appears unlikely that the influence of valerian on [GABA](#) neurotransmission contributes to central nervous system sedation [164] [165]. Valeriana officinalis extracts significantly displaced fluorodiazepam from benzodiazepine receptors, and a fraction containing sesquiterpene alcohols and ketones showed 80% inhibition

at concentrations of 1.5×10^{-3} moles/liter. A fraction containing valepotriates also produced significant displacement. Statistical values were not provided [166]. In local cerebral glucose utilization, valerian extracts reacted in a way analogous to that observed with the GABA agonist, progabide. Therefore, the interaction at the GABA-A-benzodiazepine receptor complex may differ from that of diazepam [167]. Valerian extracts inhibit (3H)flunitrazepam binding to benzodiazepine receptors; however, the amount of benzodiazepine-like molecules present in the plants is below pharmacologically-active doses [168].

c) Hydroalcoholic and aqueous extracts of *Valeriana officinalis* roots showed affinity for the GABA-A receptors with lesser affinity for the peripheral benzodiazepine receptors in vitro. Inhibition of 3H-PK 11195 binding to benzodiazepine and GABA-A receptors was measured and expressed as IC₅₀ values. IC₅₀ values for the hydroalcoholic extract were 0.04 milligrams/milliliter (mg/ml) and 3.9×10^{-3} mg/ml for peripheral and central benzodiazepine receptors and GABA-A receptors, respectively. The lipophilic fraction of the hydroalcoholic extract showed affinity for the barbiturate receptor and to some extent for peripheral benzodiazepine receptors. The aqueous total extract A, the aqueous fraction B derived from the hydroalcoholic extracts, as well as the hydroalcoholic extracts demonstrated affinity for GABA-A receptors. This interaction at the receptor level could represent the molecular basis for the sedative effect noted with *Valeriana officinalis* [169].

3.5.1.PU] Vandetanib

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

2) Summary: Concomitant use of amitriptyline and vandetanib, both drugs that prolong the QT interval, is not recommended due to the potential for additive effects on QT interval prolongation and an increased risk of serious ventricular arrhythmias. If these drugs must be used concurrently, more frequent ECG monitoring should be performed. If the corrected QT interval (Fridericia; QTcF) is greater than 500 milliseconds, discontinue therapy until QTcF returns to less than 450 milliseconds and then resume at a reduced dose[410].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of amitriptyline and vandetanib, both drugs that prolong the QT interval, is not recommended due to the potential for additive effects on QT interval prolongation and an increased risk of serious ventricular arrhythmias. If these drugs must be used concurrently, more frequent ECG monitoring should be performed. If the corrected QT interval (Fridericia; QTcF) is greater than 500 milliseconds, discontinue therapy until QTcF returns to less than 450 milliseconds and then resume at a reduced dose[410].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.PV] Vardenafil

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

2) Summary: Both amitriptyline and vardenafil have been associated with QT interval prolongation[236][326][327]. Due to the potential for additive effects on QT interval prolongation and an increased risk of torsade de pointes, caution is advised using vardenafil and drugs that prolong the QT interval, such as amitriptyline, concomitantly [327]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

- 6) Clinical Management: Concomitant use of [amitriptyline](#) and [vardenafil](#) may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), and therefore caution is advised[326][327]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.PW] [Vasopressin](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants and [vasopressin](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[938][939][940][941][942][943][944][945][946][947]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as tricyclic antidepressants and [vasopressin](#), is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.PX] [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](#)[276].
- 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](#)[276].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.PY] [Venlafaxine](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)) and adverse effects of both drugs
- 2) Summary: Tricyclic antidepressants (TCAs) and [venlafaxine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[900][901]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [venlafaxine](#), is not recommended [902]. In addition, [venlafaxine](#) and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [903][900][904]. [Venlafaxine](#) increased the AUC, Cmax, and Cmin of [desipramine](#) by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with [venlafaxine](#) 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected [899].
- 3) Severity: major
- 4) Onset: rapid

5J) Substantiation: theoretical

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

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

8J) Literature Reports

aJ) When administered with [imipramine](#), the pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected. [Venlafaxine](#) increased the area under the concentration-time curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}) of [desipramine](#) by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold ([venlafaxine](#) 37.5 mg every 12 hours) and by 4.5-fold ([venlafaxine](#) 75 mg every 12 hours). The clinical significance of this finding is unknown [899].

3.5.1.PZJ Vilanterol

1J) Interaction Effect: an increased risk of cardiovascular adverse effects

2J) Summary: Concurrent administration of vilanterol with a tricyclic antidepressant (TCA) may potentiate the adrenergic effects of vilanterol on the cardiovascular system. Therefore, extreme caution is advised if vilanterol is administered to patients who are being treated with a TCA or within 2 weeks of TCA discontinuation[893]. If coadministration is required, monitor patients closely for adverse cardiovascular effects.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use extreme caution when vilanterol is administered concurrently with a tricyclic antidepressant (TCA), or within 2 weeks of discontinuation of a TCA, due to potentiation of adrenergic-induced cardiovascular effects[893]. If coadministration is necessary, monitor patients closely for adverse cardiovascular effects.

7J) Probable Mechanism: potentiation of adrenergic agonist effects on the cardiovascular system

3.5.1.QAJ Vilazodone

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

2J) Summary: [Serotonin syndrome](#) has been reported with vilazodone monotherapy and in combination with other serotonergic drugs; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#)[279]. 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 [240]. 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 [279].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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[279].

7J) Probable Mechanism: additive serotonergic effects

3.5.1.QB| Vinflunine

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

2J) 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[319]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring when vinflunine is coadministered with other QT-prolonging agents.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant administration of vinflunine and QT-prolonging drugs may result in additive QT-interval prolongation effects and is therefore not recommended[319]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

7J) Probable Mechanism: additive QT interval effects

3.5.1.QC| Voriconazole

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

2J) Summary: Use caution when using [amitriptyline](#) and [voriconazole](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[396].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when using [amitriptyline](#) and [voriconazole](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[396].

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

3.5.1.QD| Vortioxetine

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

2J) 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[535].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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[535].

7) Probable Mechanism: additive serotonergic effects

3.5.1.QE] [Warfarin](#)

1) Interaction Effect: decreased anticoagulant effectiveness

2) Summary: [Chlordiazepoxide](#) may cause a decreased prothrombin time response when given concurrently with [warfarin](#)[212]. However, other studies have not identified an alteration in the anticoagulant effect of [warfarin](#) when given with [chlordiazepoxide](#) [213][214][215].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: In patients receiving [chlordiazepoxide](#) and [warfarin](#) concurrently, the prothrombin time ratio or INR ([international normalized ratio](#)) should be closely monitored for stability of the anticoagulant response. [Warfarin](#) dosage may require adjustment to maintain the desired level of [anticoagulation](#).

7) Probable Mechanism: unknown

3.5.1.QF] [Warfarin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[607][608]. Considerable interindividual differences may be found [609].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In patients receiving [amitriptyline](#) and [warfarin](#) concurrently, the prothrombin time ratio or INR ([international normalized ratio](#)) should be closely monitored for stability of the anticoagulant response. [Warfarin](#) dosage may require adjustment to maintain the desired level of [anticoagulation](#).

7) Probable Mechanism: decreased [warfarin](#) metabolism; increased [warfarin](#) absorption

8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of [nortriptyline](#) or [amitriptyline](#) resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects [604]. This effect was not observed with [warfarin](#).

b) A single oral dose of bishydroxycoumarin after eight days of [nortriptyline](#) resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in six healthy volunteers [605]. The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term [anticoagulant therapy](#) who used concurrent TCAs [606]. TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.QG] [Ziprasidone](#)

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

2J) 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[919][920]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

3J) Severity: contraindicated

4J) Onset: unspecified

5J) 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[919][920]; 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.QHJ Zolmitriptan

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

2J) Summary: Tricyclic antidepressants (TCAs) and zolmitriptan have been shown to prolong the QTc interval at the recommended therapeutic dose[923][924]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as zolmitriptan, is not recommended [925].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concurrent administration of zolmitriptan and tricyclic antidepressants is not recommended.

7J) Probable Mechanism: additive effects on QT prolongation

3.5.1.QIJ Zolpidem

1J) Interaction Effect: an increase in CNS depressant effects

2J) Summary: The concomitant use of zolpidem with drugs that have sedative or hypnotic properties at bedtime or in the middle of the night is not recommended. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem. Additionally the risk of complex behaviors such as sleep-driving (driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) is increased with concomitant use. Dosage adjustments of zolpidem and other concomitant CNS-depressants may be necessary when coadministered because of the potentially additive effects[231].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of zolpidem with drugs that have sedative or hypnotic properties at bedtime or in the middle of the night is not recommended. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem. Additionally the risk of complex behaviors such as sleep-driving (driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) is increased with concomitant use. Dosage adjustments of zolpidem and other concomitant CNS-depressants may be necessary when coadministered because of the potentially additive effects[231].

7J) Probable Mechanism: additive effects

3.5.1.QJ] Zotepine

- 1J) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2J) Summary: Several antipsychotic agents are associated with QT-interval prolongation[282][283][284][285][286]. Although no formal drug interaction studies have been done, coadministration of a tricyclic antidepressant with an antipsychotic is not recommended [287].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
- 7J) Probable Mechanism: additive cardiac effects
- 8J) Literature Reports

aJ) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [281].

3.5.1.QK] 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[968][969].
- 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[968][969].
- 7J) Probable Mechanism: additive QT prolongation

3.5.2] Drug-Food Combinations**3.5.2.A] Caffeine**

- 1J) Interaction Effect: reduced sedative and anxiolytic effects of [chlordiazepoxide](#)
- 2J) Summary: [Caffeine](#), in a dose-related manner, can counteract benzodiazepine-induced impairment (drowsiness, mental slowness) in some tasks during performance testing. Higher doses (500 mg, equivalent to 4 or more cups of brewed coffee) may interfere with anxiolytic effects, but the clinical significance is uncertain[1026][1027][1028].
- 3J) Severity: minor

- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor benzodiazepine response for desirable outcome. Reduction or elimination of [caffeine](#) exposure would be expected to restore desirable sedative effects (nighttime sedation).
- 7) Probable Mechanism: central nervous system antagonistic effects
- 8) Literature Reports

a) Eighteen normal volunteers were randomly studied after receiving 125, 250, or 500 mg of [caffeine](#), both alone and in combination with [lorazepam](#) 2.5 mg, with each subject serving as his own control. Performance testing included critical flicker fusion, verbal learning, digit-symbol substitution, symbol copying, and number cancellation. [Caffeine](#) significantly improved performance on the digit-symbol substitution test when given alone and reduced lorazepam-induced impairment during concurrent administration of both agents. In the symbol copying test, [caffeine](#) counteracted the lorazepam-induced impairment. Although normal subjects were used, [lorazepam](#) induced mood changes characterized as withdrawn, tranquil, and less anxious. The highest dose of [caffeine](#) (500 mg) also counteracted the anti-anxiety effects of [lorazepam](#). The study suggests that only moderate doses of [caffeine](#) should be combined with [lorazepam](#). It further raises the question of the potential effects of [caffeine](#) in patients taking benzodiazepines chronically [1025].

3.5.2.B) Ethanol

- 1) Interaction Effect: increased sedation
- 2) Summary: Concomitant ethanol and [chlordiazepoxide](#) therapy results in enhanced sedation. Ethanol also enhances the adverse psychomotor effects and decreases the ability to do tasks requiring alertness when combined with [chlordiazepoxide](#). Acutely, ethanol may inhibit benzodiazepine metabolism, especially in those with borderline liver disease[1011][1012][1013].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Patients receiving [chlordiazepoxide](#) should be advised against ethanol use.
- 7) Probable Mechanism: additive CNS depression

3.5.2.C) Ethanol

- 1) Interaction Effect: enhanced CNS depression and impairment of motor skills
- 2) Summary: Ethanol in combination with antidepressants may alter behavior, with the predominant effect being enhanced [impairment in psychomotor](#) performance. Almost all studies to date have evaluated the effects of the combination on motor skills, driving behavior and psychomotor skills[1020][1021][1022][1023][1024]. There are no studies evaluating respiratory response with the combination.
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Encourage abstinence from alcohol during at least the first few weeks of tricyclic administration to allow patient accommodation to potential CNS depressant effects of the tricyclic antidepressant.
- 7) Probable Mechanism: additive CNS depressant activity; impaired hepatic metabolism of the tricyclic antidepressant
- 8) Literature Reports

a)) The studies available indicate that the interaction between [amitriptyline](#) (and other antidepressants) in combination with ethanol is unpredictable. They indicate that antidepressants may enhance, prevent, or not affect the CNS depressant actions of ethanol. The most significant effect reported is enhanced CNS depression. However, there are reports that tricyclic antidepressants may actually antagonize the sedative effects of ethanol [1014].

b)) The propensity for interaction may be related to the inherent CNS depressant action of the tricyclic antidepressant, listed in one series in descending order as [amitriptyline](#), [doxepin](#), [imipramine](#), [nortriptyline](#), [desipramine](#), and [protriptyline](#) [1015].

c)) [Imipramine](#) and [amitriptyline](#) are the best documented examples of disruptions of metabolism. Clearance of [imipramine](#) was 3-fold higher in alcoholics compared with healthy volunteers [1016]. Individual case reports have documented "blackouts" following modest amounts of alcohol in combination with either [amitriptyline](#) or [imipramine](#) [1017], and reversible extrapyramidal effects (parkinsonian effects, [akathisia](#)) with [amoxapine](#) [1018].

d)) A study was performed to analyze the effects of ethanol on the pharmacokinetic and pharmacodynamics of [amitriptyline](#) in five healthy adults. A single dose of [amitriptyline](#) 25 mg was given both with and without ethanol. The dose of ethanol was adjusted to maintain a blood level of 800 to 1000 mg/L. The logarithmic mean free plasma levels of [amitriptyline](#) were increased by 204%, 186%, and 127% at 1.5, 2, and 2.5 hours after administration when given with ethanol. The [amitriptyline](#) 8-hour area under the plasma concentration curve was increased 48% by ethanol. In addition, ethanol increased the mean postural sway from 2% to 92% and decreased mean short term memory from 37% to 71% compared to [amitriptyline](#) given alone [1019].

3.5.4] Drug-Tobacco Combinations

3.5.4.A] Tobacco

1)) Interaction Effect: decreased exposure of CYP1A2 substrates

2)) Summary: Cigarette smoking releases polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism[1030][1040], which may reduce CYP1A2 substrate bioavailability. Advise patients to stop smoking during treatment with a CYP1A2 substrate due to the potential reduction in efficacy [1029]. If CYP1A2 substrate therapy is required in patients who smoke, consider monitoring for reduced efficacy [1030] and adjusting the CYP1A2 substrate dosage if needed [1031].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: CYP1A2 substrate bioavailability may be reduced with tobacco smoking. Advise patients to stop smoking during treatment due to the potential reduction in CYP1A2 substrate efficacy[1029]. If therapy with a CYP1A2 substrate is required in patients who smoke, consider monitoring for reduced efficacy [1030] and adjusting the CYP1A2 substrate dosage if needed [1031].

7)) Probable Mechanism: induction of CYP1A2-mediated metabolism by tobacco smoke

8)) Literature Reports

a)) Smoking 7 to 12 cigarettes/day produced maximum enzyme induction and a significantly lower mean [clozapine](#) concentration/dose (C/D) ratio in smokers than in nonsmokers (2.8 vs 6 nanograms/mL/mg/day), and similarly with [olanzapine](#) C/D ratio in another study (6.1 vs 12.8 nanograms/mL/mg/day). Smoking more than 12 cigarettes/day did not produce any further induction nor lower C/D ratio of [clozapine](#) or [olanzapine](#) [1032].

- b) Among patients treated with [mirtazapine](#) 30 mg/day for 4 weeks, smokers had significantly lower concentrations of S(+)-[mirtazapine](#) (23 vs 39 nmol/L) and [mirtazapine](#) S(+)/R(-) ratio (0.28 vs 0.37) than nonsmokers. These effects from smoking remained significant after multivariate analysis [1031].
- c) In patients receiving stable [clozapine](#) 100 mg/day, heavy smokers (30 or more cigarettes/day) had a significantly higher mean plasma [clozapine](#) concentration coefficient of variation (CV) than smokers (30% vs 16%); however, no difference was seen in patients receiving stable [clozapine](#) 300 or 600 mg/day in a study of patients with [schizophrenia](#) or [schizoaffective disorder](#) (N=47) [1033].
- d) In a study of patients receiving an average [clozapine](#) dose of 304 mg/day (N=18), [clozapine](#) and norclozapine (active metabolite) plasma concentrations were significantly lower in smokers (median of 25 cigarettes or 4 pipes/day) compared with nonsmokers. The [clozapine](#) plasma concentration in smokers was a significant 3.2-fold lower and norclozapine was 2.3-fold lower compared with plasma concentration in nonsmokers [1034].
- e) Induction of CYP1A2 activity by cigarette smoking significantly reduced [olanzapine](#) plasma concentrations and clinical effectiveness in smokers (10 to 40 cigarettes/day), compared with nonsmokers in a study of adults with thought disorder (N=17). After 15 days of [olanzapine](#) 10 mg/day, the dose-corrected steady-state [olanzapine](#) plasma concentration (C:D) ratio was about 5-fold lower in smokers compared with nonsmokers (1.56 vs 7.9 nanograms/mL/mg). At the same time, Brief Psychiatric Rating Scale total scores were significantly higher for nonsmokers than for smokers (30.4% vs 12.5%) and were positively correlated with the steady-state plasma [olanzapine](#) C:D ratio. Smoking induced a significant 6-fold higher level of CYP1A2 activity in smokers compared with nonsmokers and the index was closely correlated with the steady-state plasma [olanzapine](#) C:D ratio [1035].
- f) Cigarette smoking appears to release polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism. In vivo blood clearance and urine metabolite data from [caffeine](#) demethylation has clearly demonstrated the link between CYP1A2 activity and cigarette smoking, which may have clinical consequences when cigarette smoking occurs with [theophylline](#), [caffeine](#), [tacrine](#), [imipramine](#), [haloperidol](#), [pentazocine](#), [propranolol](#), or [flecainide](#) therapy [1030].
- g) In a study of healthy volunteers (N=14), chronically-exposed passive smokers had a significantly higher mean [theophylline](#) clearance of 60.1 mL/kg/hr compared with 40.9 mL/kg/hr for the nonsmokers. [1036]. However, in another study of volunteers (N=5), intense, short-term (5 days) passive smoking did not effect [theophylline](#) disposition [1037]. It was concluded that the short duration of exposure to tobacco smoke explained the lack of effect.
- h) A retrospective study of patients with [schizophrenia](#) (N=50) revealed that cigarette smokers (more than 1 pack/day) had significantly lower plasma concentrations of [haloperidol](#) (16.83 vs 28.8 nanograms/mL) and reduced [haloperidol](#) (active metabolite; 16.76 vs 34.23 nanograms/mL) and significantly increased [haloperidol](#) oral clearance (1.58 vs 1.1 L/min) compared with nonsmokers [1038].
- i) The administration of oral [imipramine](#) 3.5 mg/kg to smokers (15 cigarettes/day) resulted in significantly lower mean plasma levels of combined [imipramine](#) and desmethylinipramine when compared with nonsmokers (160 vs 290 nanograms/mL) [1039].

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

4.1] Monitoring Parameters

A)] Therapeutic

1)] Physical Findings

a)] Improvement in insomnia, feelings of guilt or worthlessness, agitation, psychic and somatic anxiety, [suicidal ideation](#) and anorexia within the first week of treatment may indicate efficacy.

B)] Toxic

1)] Laboratory Parameters

a)] Perform periodic liver function tests and blood counts in patients on prolonged treatment [17].

b)] Monitor renal function in elderly patients [17].

c)] Closely supervise hyperthyroid patients or those on thyroid medications [17].

d)] Monitor tricyclic antidepressant plasma levels if coadministered with another CYP450 2D6 inhibitor [17].

2)] Physical Findings

a)] Monitor for worsening of depression, suicidality, or unusual changes in behavior, especially during the initial few months of therapy or when the dose increases or decreases [17].

b)] Observe elderly patients closely for confusion and oversedation [17].

c)] Monitor patients with [cardiovascular disorders](#) for [arrhythmias](#), prolonged conduction time, and [tachycardia](#) [17].

4.2] Patient Instructions

A)] Chlordiazepoxide/Amitriptyline (By mouth)

[Amitriptyline Hydrochloride/Chlordiazepoxide](#)

Treats depression caused by anxiety. This medicine is a combination of a benzodiazepine and a tricyclic antidepressant (TCA).

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 [chlordiazepoxide](#), [amitriptyline](#), or similar medicines.

How to Use This Medicine:

Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

Drink extra fluids so you will urinate more often and help prevent kidney problems.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not use this medicine if you have used an MAO inhibitor within the past 14 days.

Some foods and medicines can affect how this medicine works. Tell your doctor if you are using any of the following:

[Cimetidine](#), [guanethidine](#), [topiramate](#)

Medicine for heart rhythm problem (including [flecainide](#), [propafenone](#), [quinidine](#))

Other medicine to treat depression (including [fluoxetine](#), [paroxetine](#), [sertraline](#))

Phenothiazine medicine (including [chlorpromazine](#), [prochlorperazine](#), [promethazine](#), [thioridazine](#))

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, planning to become pregnant, or breastfeeding, or if you have [kidney disease](#), liver disease, [heart](#) or [blood vessel disease](#), an [overactive thyroid](#), or a history of [glaucoma](#), seizures, or trouble urinating. Tell your doctor if you have a recent [heart attack](#).

This medicine may increase depression or thoughts of suicide. Tell your doctor right away if you start to feel more depressed or think about hurting yourself.

This medicine may cause the following problems:

Changes in heart rhythm (including [arrhythmia](#))

[Heart attack](#) or [stroke](#)

This medicine may make you dizzy or drowsy. Do not drive or do anything else that could be dangerous until you know how this medicine affects you.

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.

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

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.

Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.

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

Possible Side Effects While Using This Medicine:

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

[Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Change in how much or how often you urinate, trouble urinating
 Changes in behavior, unusual thoughts of hurting yourself or others, trouble sleeping
 Chest pain that may spread to your arms, jaw, back, or neck, trouble breathing, nausea, unusual sweating, faintness
 Fast, pounding, or uneven heartbeat
 Seizures or tremors

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

Blurred vision
 Constipation
 Dizziness or drowsiness
 Dry mouth

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

4.3] Place In Therapy

A) Depression is a complicated disorder and consequently this disease's treatment regimens are diverse. The two most prevalent diagnostic syndromes among affective disorders are [major depression](#) and [bipolar disorders](#). The tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs) are considered the most effective agents for treating [major depression](#). For treating [bipolar disorders](#), [lithium](#) is considered the standard of therapy over TCAs, MAOIs and other agents such as [carbamazepine](#) or [levothyroxine](#).

B) [Chlordiazepoxide/ amitriptyline](#) is effective for the treatment of anxiety-depression disorders. Benzodiazepines are considered effective for suppressing anticipatory anxiety associated with panic attacks, however, TCAs and MAOIs are considered the drugs of choice for controlling this disorder. [Amitriptyline](#) alone is equally effective for treating panic attacks as [chlordiazepoxide/ amitriptyline](#). The onset of action for the combination is faster than [amitriptyline](#) alone, however, the end therapeutic responses are the same.

C) [Chlordiazepoxide/ amitriptyline](#) has a place in therapy for treating anxiety-depressive disorders, but should be considered secondary to [amitriptyline](#) alone, other TCAs or MAOIs. The fixed combination limits the ability to titrate the antidepressant component separate from the anxiolytic component, and is more expensive. Since each case of anxiety-depression is unique, using a benzodiazepine independently from an antidepressant provides a more practical therapy regimen. [Chlordiazepoxide/ amitriptyline](#) is not recommended for general formulary inclusion.

4.4] Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) [Limbitrol\(R\)](#) contains [chlordiazepoxide](#), a benzodiazepine indicated for relief of anxiety and tension and [amitriptyline](#), a tricyclic antidepressant. Both components of [Limbitrol\(R\)](#) exert their principal action in the CNS. [Chlordiazepoxide](#) exhibits general benzodiazepine activity, appearing to act at the limbic level of the CNS, producing antianxiety and sedative effects. Its action may be mediated through the inhibitory neurotransmitter [gamma aminobutyric acid \(GABA\)](#). The mechanism of action of [amitriptyline](#) in man is not known, but the drug appears to interfere with the reuptake of [norepinephrine](#) into adrenergic nerve endings. This action may prolong the sympathetic activity of biogenic amines and contribute to antianxiety activity [1098].

B) REVIEW ARTICLES

1) Drug-interactions of antidepressants are reviewed in German language [1099].

4.5] Therapeutic Uses

4.5.1] FDA Uses

4.5.1.A] Mixed anxiety and depressive disorder

FDA Labeled Indication

1]) 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](#)

2]) Summary:

Many studies have suggested that patients who are depressed and anxious should receive both an antianxiety agent and an antidepressant [2][3][4][5][6]

3]) Adult:

a]) Anxiety accompanying depression can generally be relieved by antidepressant therapy alone, and antianxiety agents are not routinely required. Thus, initial treatment should not involve combination therapy [7], and initial therapy with an antidepressant alone is suggested by most clinicians. In addition, individual titration of antidepressant drugs is required in most patients to achieve optimal responses; this is more easily accomplished if antidepressants are not in a fixed-dose combination, as is [Limbital\(R\)](#) [7]. If it is determined that the optimum maintenance dose corresponds to the ratio in a commercial combination preparation, such a product may be appropriate. However, since the same dosage regimen is almost never prescribed for any 2 patients, nor for any ONE patient throughout therapy, the fixed combination appears to be impractical as well as costly.

b]) The combination of [chlordiazepoxide](#) and [amitriptyline](#) was reported to produce measurable improvement in neurotic outpatients with mixed ANXIETY DEPRESSION SYNDROMES [8]. Statistically significant differences were demonstrated in an overall assessment of patients during the first 2 weeks when the combination was compared with placebo [9][8], or [amitriptyline](#) alone [9][10][8][11][2]. However, there were no statistically significant differences after the fourth week of observation in studies comparing [amitriptyline](#) alone versus the combination [8][11][2].

c]) If [Limbital\(R\)](#) is utilized, the smallest possible effective dose of [chlordiazepoxide](#) is recommended to avoid oversedation and more importantly, dependence. With a possible maintenance dose of [amitriptyline](#) being in the range of 100 to 200 milligrams daily, the amount of [chlordiazepoxide](#) in the combination form would be 40 to 80 milligrams. Flexibility in necessary dosage adjustments is lost. Should adverse effects occur, it is not possible to adjust dosage of 1 component without changing the other.

d]) [Limbital\(R\)](#) may slightly decrease the total number of tablets to be taken daily, but the recommended dosage frequency does not change. Therefore, the potential for noncompliance is still a problem.

e]) A four-way, double-blind study involving 337 patients demonstrated [Limbital\(R\)](#) was superior to either [amitriptyline](#) or [chlordiazepoxide](#) alone in the treatment of patients with moderate to marked depression and anxiety [12]. The study lasted 4 weeks. Global physician and patient

rating scales were used to evaluate the response. The combination product produced substantially better results after 1 week than either drug alone. Discontinuation of treatment due to side effects occurred less with the combination product. Similar results accrued in a study of like design involving 279 patients [9]. Few patients required discontinuation of **Limbitrol(R)** due to side effects than either component alone.

f) A single nighttime dose was compared to a divided daily dosage of **Limbitrol(R)** (**chlordiazepoxide**, **amitriptyline** 12.5 milligrams) in mild to moderately depressed patients. Both groups showed significant improvement over the 3-week study period [13].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] **Amitriptyline**

4.6.A.1] Depression

a) SUMMARY:

b) Equally effective for depression

c) **Limbitrol(R)** (**amitriptyline** 25 milligrams (mg) plus **chlordiazepoxide** 10 mg) was as effective as oral **amitriptyline** 25 mg when each were given as single nighttime doses for the treatment of depression with anxiety in a controlled study [1100]. Patients were administered 1 to 4 capsules nightly for 28 days. There was no difference between the 2 treatments, but significantly more patients receiving **Limbitrol(R)** demonstrated improvement after 7 days of therapy. This difference was only significant when the number of improved patients was used as a measure of efficacy. Improvement was defined as a score of less than 16 on the Hamilton Rating Scale. Overall, the 2 drugs were similar in efficacy.

d) SUMMARY:

Equally effective for depression

Cianopramine may have fewer cardiac adverse effects

e) **Amitriptyline** (50 to 150 milligrams (mg)/day) was compared to cianopramine (2 to 6 mg/day) in a double-blind, placebo-controlled, parallel, 4-week study of 60 patients with depression. The two drugs were judged to be equally efficacious and superior to placebo. Cianopramine caused significantly fewer anticholinergic side effects compared to **amitriptyline** [1101].

f) The combination of **amitriptyline** and **chlordiazepoxide** was compared against each component alone. The patient population was differentiated into "high" and "low" anxious and "high" and "low" depressive subgroups. **Amitriptyline** alone was more effective in the more depressed, less anxious patients; **chlordiazepoxide** alone produced the most improvement in the low depressed, highly anxious patients. The drug combination was particularly effective in the highly depressed, highly anxious patient [1103].

g) In a multicenter trial, **Limbitrol(R)** was compared to its components, **amitriptyline** and **chlordiazepoxide**, in the treatment of 337 patients with **depressive illness** [1104]. Patient improvement over time was assessed by the following: the Hamilton Depression Scale, the Physicians Global Evaluation, the Patients Global Evaluation, and the **Beck Depression Inventory**. The combination drug was significantly more effective than **chlordiazepoxide** alone after 2 weeks, and significantly more effective than **amitriptyline** alone during the first 2 weeks of the study. The study was conducted over a period of only 4 weeks and the average antidepressant takes 21 days to produce an initial response [1105].

h) **Limbitrol(R)** (**amitriptyline** 25 mg plus **chlordiazepoxide** 10 mg) was as effective as oral **amitriptyline** 25 mg when each were given as single nighttime doses for the treatment of depression with anxiety in a controlled study [1106]. Patients were administered 1 to 4 capsules nightly for 28 days. There was no difference between the 2 treatments, but significantly more patients receiving **Limbitrol(R)** demonstrated improvement after 7 days of therapy. This difference was only significant when the number of improved

patients was used as a measure of efficacy. Improvement was defined as a score of less than 16 on the Hamilton Rating Scale. Overall, the 2 drugs were similar in efficacy.

4.6.A.2) Adverse Effects

a) **Amitriptyline** may aggravate **ischemic heart disease** and rhythm disorders while cianopramine may be preferred in patients with **heart disease** [1102]. Cardiovascular effects of **amitriptyline** 75 to 150 milligrams (mg)/day were compared to cardiovascular effects of cianopramine 6 to 12 mg/day in 23 patients with major **depressive illness** but without significant **cardiovascular disease**. **Amitriptyline** had a significantly greater adverse effect on cardiac cycle time intervals and the **electrocardiogram**. There was no significant difference between the drugs in terms of effects on blood pressure.

4.6.B) Chlordiazepoxide

4.6.B.1) Depression

a) The combination of **amitriptyline** and **chlordiazepoxide** was compared against each component alone. The patient population was differentiated into "high" and "low" anxious and "high" and "low" depressive subgroups. **Amitriptyline** alone was more effective in the more depressed, less anxious patients; **chlordiazepoxide** alone produced the most improvement in the low depressed, highly anxious patients. The drug combination was particularly effective in the highly depressed, highly anxious patient [1103].

b) In a multicenter trial, **Limbitrol(R)** was compared to its components, **amitriptyline** and **chlordiazepoxide**, in the treatment of 337 patients with **depressive illness** [1104]. Patient improvement over time was assessed by the following: the Hamilton Depression Scale, the Physicians Global Evaluation, the Patients Global Evaluation, and the **Beck Depression Inventory**. The combination drug was significantly more effective than **chlordiazepoxide** alone after 2 weeks, and significantly more effective than **amitriptyline** alone during the first 2 weeks of the study. The study was conducted over a period of only 4 weeks and the average antidepressant takes 21 days to produce an initial response [1105].

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