

DRUGDEX-EV 2570

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**DOXEPIN**

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**0.0] Overview**

**1] Class**

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

Antianxiety  
Antidepressant  
Antiulcer  
Dermatological Agent  
Sleep Aid

**2] Dosing Information**

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

**1] Adult**

**a)** Alcoholism - Anxiety - Depression

**1)** (Capsules, concentrate) Initial, 75 mg/day orally for mild to moderate severity illness; very mild severity illness may be controlled with 25 to 50 mg/day orally. Titration, may gradually increase to 300 mg/day orally with more severe illness; additional therapeutic effect is rarely obtained above 300 mg/day. Usual dosage, 75 to 150 mg orally daily in a single or divided doses; MAX 150 mg/day if given on a once-daily schedule [2][3]

**b)** Anxiety

**1)** (Capsules, concentrate) Initial, 75 mg/day orally for mild to moderate severity illness; very mild severity illness may be controlled with 25 to 50 mg/day orally. Titration, may gradually increase to 300 mg/day orally with more severe illness; additional therapeutic effect is rarely obtained above 300 mg/day. Usual dosage, 75 to 150 mg orally daily in a single or divided doses; MAX 150 mg/day if given on a once-daily schedule [2][3]

**c)** Depression

**1j)** (Capsules, concentrate) Initial, 75 mg/day orally for mild to moderate severity illness; very mild severity illness may be controlled with 25 to 50 mg/day orally. Titration, may gradually increase to 300 mg/day orally with more severe illness; additional therapeutic effect is rarely obtained above 300 mg/day. Usual dosage, 75 to 150 mg orally daily in a single or divided doses; MAX 150 mg/day if given on a once-daily schedule [2][3]

**dj)** Depression - **Psychotic disorder**

**1j)** (Capsules, concentrate) Initial, 75 mg/day orally for mild to moderate severity illness; very mild severity illness may be controlled with 25 to 50 mg/day orally. Titration, may gradually increase to 300 mg/day orally with more severe illness; additional therapeutic effect is rarely obtained above 300 mg/day. Usual dosage, 75 to 150 mg orally daily in a single or divided doses; MAX 150 mg/day if given on a once-daily schedule [2][3]

**ej)** Insomnia, Characterized by difficulty with sleep maintenance

**1j)** (Silenor(R), less than 65 years) 6 mg orally once daily within 30 minutes of bedtime; 3 mg once daily may be appropriate in some patients; MAX 6 mg/day [22]

**2j)** (Silenor(R), 65 years or older) Initial, 3 mg orally once daily within 30 minutes of bedtime; may increase to 6 mg once daily; MAX 6 mg/day [22]

**fj)** **Pruritus** (Moderate), Due to **atopic dermatitis** or **lichen simplex chronicus**

**1j)** (Topical cream) Apply a thin film of 5% cream to skin 4 times daily, with at least 3 hours between applications; MAX duration, 8 days (FDA dosage) [39]

**2j)** (Topical cream) Apply 5% cream to skin in combination with 2.5% hydrocortisone or 0.1% triamcinolone cream 4 times daily for up to 8 days (off-label dosage) [40]

**2j)** Pediatric

**aj)** **Safety and effectiveness not established in pediatric patients [2][3][39][22]**

**1j)** Alcoholism - Anxiety - Depression

**aj)**(Capsules and concentrate, 12 years or older) Initial, 75 mg/day orally for mild to moderate severity illness; very mild severity illness may be controlled with 25 to 50 mg/day orally. Titration, may gradually increase to 300 mg/day orally with more severe illness; additional therapeutic effect is rarely obtained above 300 mg/day. Usual dosage, 75 to 150 mg orally daily in a single or divided doses; MAX 150 mg/day if given on a once-daily schedule [2][3]

**2j)** Anxiety

**aj)** (Capsules and concentrate, 12 years or older) Initial, 75 mg/day orally for mild to moderate severity illness; very mild severity illness may be controlled with 25 to 50 mg/day orally. Titration, may gradually increase to 300 mg/day

orally with more severe illness; additional therapeutic effect is rarely obtained above 300 mg/day. Usual dosage, 75 to 150 mg orally daily in a single or divided doses; MAX 150 mg/day if given on a once-daily schedule [2][3]

### 3) Depression

**a)** (Capsules and concentrate, 12 years or older) Initial, 75 mg/day orally for mild to moderate severity illness; very mild severity illness may be controlled with 25 to 50 mg/day orally. Titration, may gradually increase to 300 mg/day orally with more severe illness; additional therapeutic effect is rarely obtained above 300 mg/day. Usual dosage, 75 to 150 mg orally daily in a single or divided doses; MAX 150 mg/day if given on a once-daily schedule [2][3]

### 4) Depression - Psychotic disorder

**a)** (Capsules and concentrate, 12 years or older) Initial, 75 mg/day orally for mild to moderate severity illness; very mild severity illness may be controlled with 25 to 50 mg/day orally. Titration, may gradually increase to 300 mg/day orally with more severe illness; additional therapeutic effect is rarely obtained above 300 mg/day. Usual dosage, 75 to 150 mg orally daily in a single or divided doses; MAX 150 mg/day if given on a once-daily schedule [2][3]

### 3) Contraindications

#### **a)** Doxepin Hydrochloride

- 1) Coadministration with or within 2 weeks of an MAOI [22]
- 2) Glaucoma [43]
- 3) Glaucoma, untreated narrow angle [22][44]
- 4) Hypersensitivity to doxepin, any component of the product [43][22][44], or other dibenzoxepines [22]
- 5) Urinary retention, tendency towards [43][44] or severe [22]

### 4) Serious Adverse Effects

#### **a)** Doxepin Hydrochloride

- 1) Agranulocytosis
- 2) Anemia
- 3) Hypotension
- 4) Leukopenia
- 5) Nephrotoxicity

- 6j) Sudden cardiac death
- 7j) Suicidal thoughts
- 8j) Suicide
- 9j) [Thrombocytopenia](#)
- 10j) [Ventricular arrhythmia](#)

## 5j) Clinical Applications

### aj) [Doxepin](#) Hydrochloride

#### 1j) FDA Approved Indications

- a) Alcoholism - Anxiety - Depression
- b) Anxiety
- c) Depression
- d) Depression - [Psychotic disorder](#)
- e) Insomnia, Characterized by difficulty with sleep maintenance
- f) [Pruritus](#) (Moderate), Due to [atopic dermatitis](#) or [lichen simplex chronicus](#)

## 1.0j Dosing Information

[Drug Properties](#)

[Storage and Stability](#)

[Adult Dosage](#)

[Pediatric Dosage](#)

### 1.1j Drug Properties

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

Bj) Synonyms

[Doxepin](#)

[Doxepin](#) HCl

[Doxepin](#) Hydrochloride

Cj) Physicochemical Properties

1j) Molecular Weight

a) Hydrochloride: 315.84 [22]

2j) Solubility

a) Readily soluble in water [22]

## 1.2] Storage and Stability

### A) Doxepin Hydrochloride

#### 1) Preparation

##### a) Oral route

##### 1) Oral Concentrate

a) Dilute with 120 mL water, milk, or orange, grapefruit, tomato, prune or pineapple juice just prior to administration. Do not dilute in carbonated beverages [42].

##### 2) Silenor(R) Tablet

a) Do not take within 3 hours of a meal to minimize the risk of next day effects [22].

##### b) Topical application route

##### 1) Administration

a) Apply thin film to affected area. Do not use occlusive dressings [39].

### B) Oral route

#### 1) Tablet

a) Store at controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F). Protect from light [22].

### C) Topical application route

#### 1) Cream

a) Store at or below 27 degrees C (80 degrees F) [44].

## 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] Doxepin Hydrochloride

**1.3.1.B.1] Oral route****1.3.1.B.1.a] Alcoholism - Anxiety - Depression****1]) Oral Capsules and Concentrate**

**a])** Initial dosage: Mild to moderate severity symptoms, 75 mg orally daily; very mild symptoms may be controlled with doses as low as 25 to 50 mg/day [2][3]

**b])** Titration: May gradually titrate up to 300 mg/day orally if necessary in more severely ill patients; additional therapeutic effect is rare at dosages exceeding 300 mg/day [2][3].

**c])** Usual dosage: 75 to 150 mg orally daily in single or divided doses; if once daily dosing, do not exceed 150 mg [2][3]

**1.3.1.B.1.b] Anxiety****1]) Oral Capsules and Concentrate**

**a])** Initial dosage: Mild to moderate severity symptoms, 75 mg orally daily; very mild symptoms may be controlled with doses as low as 25 to 50 mg/day [2][3]

**b])** Titration: May gradually titrate up to 300 mg/day orally if necessary in more severely ill patients; additional therapeutic effect is rare at dosages exceeding 300 mg/day [2][3].

**c])** Usual dosage: 75 to 150 mg orally daily in single or divided doses; if once daily dosing is used, do not exceed 150 mg [2][3]

**1.3.1.B.1.c] Depression****1]) Oral Capsules and Concentrate**

**a])** Initial dosage: Mild to moderate severity symptoms, 75 mg orally daily; very mild symptoms may be controlled with doses as low as 25 to 50 mg/day [2][3].

**b])** Titration: May gradually titrate up to 300 mg/day orally if necessary in more severely ill patients; additional therapeutic effect is rare at dosages exceeding 300 mg/day [2][3].

**c])** Usual dosage: 75 to 150 mg orally daily in single or divided doses; if once daily dosing, do not exceed 150 mg [2][3]

**1.3.1.B.1.d] Depression - Psychotic disorder****1]) Oral Capsules and Concentrate**

**a])** Initial dosage: Mild to moderate severity symptoms, 75 mg orally daily; very mild symptoms may be controlled with doses as low as 25 to 50 mg/day [2][3]

**b])** Titration: May gradually titrate up to 300 mg/day orally if necessary in more severely ill patients; additional therapeutic effect is rare at dosages exceeding 300 mg/day [2][3].

**c])** Usual dosage: 75 to 150 mg orally daily in single or divided doses; if once daily dosing, do not exceed 150 mg [2][3]

**1.3.1.B.1.e] Insomnia, Characterized by difficulty with sleep maintenance****1]) Silenor(R) Tablet**

**a])** Usual dosage (Younger than 65 years): 6 mg orally once daily 30 minutes prior to bedtime; 3 mg once daily may be appropriate in some patients [22].

**b])** Usual dosage (65 years or older): Begin with 3 mg orally once daily 30 minutes prior to bedtime; may increase to 6 mg once daily [22].

**c])** Maximum dosage: Do not exceed 6 mg daily [22]

**1.3.1.B.1.f] Urticaria**

**1])** Doxepin in doses of 10 to 30 milligrams orally daily has been effective in the treatment of IDIOPATHIC COLD URTICARIA [6].

**2])** Doxepin 5 milligrams orally twice daily was reported effective in the treatment of chronic idiopathic URTICARIA in a controlled study [7][8].

**3])** Doxepin 25 milligrams orally three times daily was effective in the treatment of CHRONIC IDIOPATHIC URTICARIA in a placebo-controlled trial involving 16 adult patients [9].

**1.3.1.B.2] Topical application route****1.3.1.B.2.a] Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus****1]) FDA Dosage, Topical Cream**

**a])** Usual dosage, 5% cream apply a thin film 4 times a day, with at least 3 to 4 hour intervals between applications [39]

**b])** Duration: Not to exceed 8 days of use [39].

**2]) Off-Label Dosage, Topical Cream**

**a])** Apply 5% doxepin cream in combination with 2.5% hydrocortisone or 0.1% triamcinolone cream 4 times daily for up to 8 days [40].

**1.3.1.B.3])** The safety and effectiveness of doxepin hydrochloride have not been established in pediatric patients [2][3][39][22].

**1.3.3] Dosage in Hepatic Insufficiency****A]) Doxepin Hydrochloride**

**1])** Initial dosage for the treatment of insomnia is 3 mg orally once daily 30 minutes prior to bedtime [22].

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

**1])** Initial dosage for the treatment of insomnia is 3 mg orally once daily 30 minutes prior to bedtime; however, the dosage may be titrated to 6 mg once daily if clinically indicated [22].

**2])** Start at the lower end of the dosing range [2][39][3]

### 1.3.6] Dosage in Other Disease States

#### A) Doxepin Hydrochloride

- 1) Urinary retention: Initial dosage for the treatment of insomnia is 3 mg orally once daily 30 minutes prior to bedtime [22]
- 2) Drowsiness in atopic dermatitis or lichen simplex chronicus: Reduction in number of topical applications per day, body surface area treated, total amount applied, or discontinuation may be necessary [39].

### 1.4] Pediatric Dosage

#### 1.4.1] Normal Dosage

##### 1.4.1.A] Important Note

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

##### 1.4.1.B] Doxepin Hydrochloride

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

###### 1.4.1.B.1.a] Alcoholism - Anxiety - Depression

###### 1) 12 Years or Older, Oral Capsules and Concentrate

- a) Initial dosage: Mild to moderate severity symptoms, 75 mg orally daily; very mild symptoms may be controlled with doses as low as 25 to 50 mg/day [2][3]
- b) Titration: May gradually titrate up to 300 mg/day orally if necessary in more severely ill patients; additional therapeutic effect is rare at dosages exceeding 300 mg/day [2][3].
- c) Usual dosage: 75 to 150 mg orally daily in single or divided doses; if once daily dosing, do not exceed 150 mg [2][3]

###### 1.4.1.B.1.b] Anxiety

###### 1) 12 Years or Older, Oral Capsules and Concentrate

- a) Initial dosage: Mild to moderate severity symptoms, 75 mg orally daily; very mild symptoms may be controlled with doses as low as 25 to 50 mg/day [2][3]
- b) Titration: May gradually titrate up to 300 mg/day orally if necessary in more severely ill patients; additional therapeutic effect is rare at dosages exceeding 300 mg/day [2][3].
- c) Usual dosage: 75 to 150 mg orally daily in single or divided doses; if once daily dosing is used, do not exceed 150 mg [2][3]

###### 1.4.1.B.1.c] Depression

###### 1) 12 Years or Older, Oral Capsules and Concentrate

- a) Initial dosage: Mild to moderate severity symptoms, 75 mg orally daily; very mild symptoms may be controlled with doses as low as 25 to 50 mg/day [2][3]



**b)** Titration: May gradually titrate up to 300 mg/day orally if necessary in more severely ill patients; additional therapeutic effect is rare at dosages exceeding 300 mg/day [2][3].

**c)** Usual dosage: 75 to 150 mg orally daily in single or divided doses; if once daily dosing, do not exceed 150 mg [2][3]

#### **1.4.1.B.1.d] Depression - Psychotic disorder**

##### **1)] 12 Years or Older, Oral Capsules and Concentrate**

**a)** Initial dosage: Mild to moderate severity symptoms, 75 mg orally daily; very mild symptoms may be controlled with doses as low as 25 to 50 mg/day [2][3]

**b)** Titration: May gradually titrate up to 300 mg/day orally if necessary in more severely ill patients; additional therapeutic effect is rare at dosages exceeding 300 mg/day [2][3].

**c)** Usual dosage: 75 to 150 mg orally daily in single or divided doses; if once daily dosing, do not exceed 150 mg [2][3]

## **2.0] Pharmacokinetics**

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

### **2.1] Onset and Duration**

#### **A)] Onset**

##### **1)] Doxepin Hydrochloride**

##### **a)] Peak Response**

**1)] Depression, oral: 2 to 3 weeks [42].**

**a)] Optimal antidepressant effect may not be evident for 2 to 3 weeks [42].**

**2)] Anxiety, oral: 5 to 6 days (Pereira & Lipke, 1970)[773].**

**3)] Anti-anxiety effect is evident within 5 to 6 days (Pereira & Lipke, 1970)[773].**

### **2.2] Drug Concentration Levels**

#### **A)] Doxepin Hydrochloride**

##### **1)] Therapeutic Drug Concentration**

**a)] Depression: greater than 100 nanograms/mL (parent compound with active metabolite, desmethyldoxepin) [775].**

1j) A therapeutic concentration greater than 100 nanograms/mL (parent compound with active metabolite, desmethyldoxepin) is suggested for treatment of depression [775].

2j) Other studies have found no correlation between serum concentration and therapeutic response [776][777][778].

3j) Therapeutic response has been associated with 20 nanograms/mL or above of the active metabolite desmethyldoxepin [779].

4j) For both doxepin and its active metabolite, desmethyldoxepin, plasma concentrations are highly variable and are poorly correlated with dosage [44].

5j) In 19 patients with pruritic eczema treated with topical doxepin, plasma doxepin concentrations ranged from nondetectable to 47 nanograms per mL [44].

## 2j) Peak Concentration

a) Increases in C<sub>max</sub> were approximately dose-proportional following oral administration of doxepin hydrochloride 3 mg and 6 mg [22].

## 3j) Time to Peak Concentration

a) Oral: 3.5 hr [22].

1j) Median T<sub>max</sub> following oral administration of doxepin hydrochloride 6 mg to fasted healthy subjects was 3.5 hours [22].

b) Topical: 1.32 hr [774].

1j) Time to peak concentration was 1.32 hours with a maximum concentration of 0.41 mcg/L in 12 subjects with pruritic atopic dermatitis who applied topical doxepin 4 times daily every 4 hours for 7 days [774].

## 2.3] ADME

### 2.3.1] Absorption

#### Aj) Doxepin Hydrochloride

##### 1j) Effects of Food

a) Increased AUC and C<sub>max</sub>; T<sub>max</sub> delayed [22]

1j) Compared to oral administration in the fasted state, the AUC and C<sub>max</sub> were increased by 41% and 15%, respectively, and the T<sub>max</sub> was delayed by approximately 3 hours when doxepin 6 mg was administered with a high fat meal. When treating

insomnia, doxepin should not be taken within 3 hours of a meal to allow for faster onset and to minimize the potential for next day effects [22].

### 2.3.2] Distribution

#### A) Distribution Sites

##### 1) Doxepin Hydrochloride

###### a) Protein Binding

###### 1) plasma proteins: 80% [22]

a) The protein binding of doxepin is approximately 80% to plasma proteins [22].

###### b) Tissues and Fluids

1) Tissues, initially high in the liver, kidney, spleen and lung. Large amounts of the active metabolite (desmethyldoxepin) also found in tissues [780].

2) Doxepin is widely distributed throughout body tissues including lungs, heart, brain, and liver [44].

#### B) Distribution Kinetics

##### 1) Doxepin Hydrochloride

###### a) Volume of Distribution

###### 1) 11,930 L [22]

a) Doxepin is widely distributed with a mean apparent Vd of 11,930 L following single oral administration of doxepin 6 mg in healthy subjects [22].

### 2.3.3] Metabolism

#### A) Metabolism Sites and Kinetics

##### 1) Doxepin Hydrochloride

###### a) Liver: extensive [22]

1) Following absorption into systemic circulation, doxepin hydrochloride is extensively metabolized in the liver via oxidation and demethylation to its primary metabolite, N-desmethyldoxepin (nordoxepin). The primary metabolite undergoes further glucuronidation prior to excretion of both the parent and its metabolites in the urine. In vitro studies have shown CYP2C19 and CYP2D6 are the major enzymes

involved in doxepin hydrochloride metabolism and CYP1A2 and CYP2C9 have lesser involvement [22][44]

**B)) Metabolites**

**1)) Doxepin Hydrochloride**

**a)) N-desmethyldoxepin (nordoxepin): active [22][44].**

**1))** N-desmethyldoxepin (nordoxepin) is the primary pharmacologically active metabolite of doxepin [22][44].

**2.3.4] Excretion**

**A)) Kidney**

**1)) Doxepin Hydrochloride**

**a)) Renal Excretion (%)**

**1))** Doxepin hydrochloride is excreted in the urine mainly as glucuronide conjugates. Less than 3% of the dose is excreted as parent compound or N-desmethyldoxepin [22].

**2.3.5] Elimination Half-life**

**A)) Parent Compound**

**1)) Doxepin Hydrochloride**

**a)) 15.3 hr [22]**

**1))** The apparent elimination half-life of doxepin hydrochloride is 15.3 hr [22].

**B)) Metabolites**

**1)) Doxepin Hydrochloride**

**a)) Desmethyldoxepin, 31 hr [22]**

**1))** The apparent elimination half-life of desmethyldoxepin is 31 hr [22].

**2))** The half-life of desmethyldoxepin ranges from 28 to 52 hours and is not affected by multiple dosing [44]

**2.3.6] Extracorporeal Elimination**

**A)) Hemodialysis**

**1)) Doxepin Hydrochloride**

a) Dialyzable: No[781]

1) Only 7.6% of doxepin hydrochloride and 13.9% of desmethyldoxepin is extracted by hemodialysis [782].

B) Peritoneal

1) Doxepin Hydrochloride

a) Dialyzable: No[781]

1) Doxepin hydrochloride is not significantly removed by peritoneal dialysis [781].

### 3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

#### 3.0.A] Black Box WARNING

Doxepin Hydrochloride

Oral (Capsule; Solution)

##### Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of doxepin hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults 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. Doxepin hydrochloride is not approved for use in pediatric patients [43].

### 3.1] Contraindications

A) Doxepin Hydrochloride

- 1) Coadministration with or within 2 weeks of an MAOI [22]
- 2) [Glaucoma](#) [43]
- 3) [Glaucoma](#), untreated narrow angle [22][44]
- 4) Hypersensitivity to [doxepin](#), any component of the product [43][22][44], or other dibenzoxepines [22]
- 5) Urinary retention, tendency towards [43][44] or severe [22]

### 3.2] Precautions

#### A) [Doxepin](#) Hydrochloride

- 1) Black box warning: Increased risk of new or worsening suicidality, especially in children (unapproved use), adolescents, and young adults; monitoring recommended, particularly during the first few months of therapy or following dose adjustments; discontinuation may be required [43][22]
- 2) Concomitant use: Avoid with alcohol [22]
- 3) Beers Criteria: Avoid use in older adults due to highly anticholinergic and sedating effects, and risk of orthostatic hypotension (safety profile of low-dose [doxepin](#) 6 mg/day or less is comparable to placebo). In particular, avoid in older adults with a history of falls or fractures (unless safer alternatives are not available) as ataxia, impaired psychomotor function, syncope, and additional falls may occur, patients with or at high risk for [delirium](#) as [delirium](#) may occur or worsen, patients with [dementia](#) or cognitive impairment due to adverse CNS effects, patients at risk for syncope as orthostatic hypotension or bradycardia may occur, and in men with lower urinary tract symptoms or [benign prostatic hyperplasia](#) as decreased urinary flow and urinary retention may occur. If prescribed, use caution as SIADH or [hyponatremia](#) may occur or be exacerbated. Monitor sodium levels when starting or changing doses [1].
- 4) Concomitant use: Avoid initiating therapy for at least 5 weeks after [fluoxetine](#) discontinuation; monitoring recommended [43]
- 5) Concomitant use: Avoid concomitant use of MAOIs or use of [doxepin](#) within 14 days of MAOI discontinuation [43][44]
- 6) Dermatologic: Avoid use of [occlusive dressing](#) with topical use due to risk of increased absorption [44]
- 7) Neurologic: Complex sleep-related behaviors may occur, including activities performed while asleep with no recall (eg, sleep-driving, making phone calls, preparing and eating food); increased risk with concomitant use of alcohol or other CNS depressants [22]
- 8) Ophthalmic: Worsening of [angle-closure glaucoma](#) may occur in patients with anatomically narrow angle without a patent [iridectomy](#) [43]
- 9) Psychiatric: Antidepressant therapy may trigger a mixed/[manic episode](#) in patients with underlying [bipolar disorder](#); baseline screening recommended [43]
- 10) Psychiatric: Dose reduction may be required if mania or [psychosis](#) occur [43]
- 11) Psychiatric: Consider comorbid physical or psychiatric disorders with insomnia that fails to remit after 7 to 10 days or with emergence of new behavioral or cognitive abnormalities [22]

12J) Respiratory: Use not recommended in patients with severe [sleep apnea](#) [22]

### 3.3] Adverse Reactions

#### 3.3.1] Cardiovascular Effects

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

###### 3.3.1.A.1] [Cardiac dysrhythmia](#)

aJ) A systematic study of the cardiovascular effects of [doxepin](#) was conducted in depressed patients with preexisting [cardiovascular disease](#). [Doxepin](#) had little effect on heart rate and did not adversely affect left ventricular function, but did have a significant antiarrhythmic effect, slowed cardiac conduction, and caused a significant increase in orthostatic hypotension. Five (16%) of the 32 patients dropped out of the study due to cardiovascular effects. The authors concluded that [doxepin](#) provided no more cardiovascular safety than [imipramine](#) or [nortriptyline](#) [52].

bJ) In a comparison of the cardiovascular effects of [maprotiline](#) (75 to 225 mg/day) with [doxepin](#) (50 to 200 mg/day) in 49 elderly depressed patients, there were no significant differences in orthostatic hypotension. [Maprotiline](#) caused fewer [premature ventricular contractions](#) (PVCs) and a longer PRS interval. Both drugs had a small but significant effect on heart rate and PR interval [53].

cJ) [Ventricular arrhythmias](#) associated with [doxepin](#) and [amitriptyline](#) occurred in a 57-year-old man with preexisting [heart disease](#). The patient was treated with a total [doxepin](#) dose of 250 mg/day, and after discontinuation of the cardiac medications, he developed a quadrigeminy pattern of [ventricular premature depolarizations](#) (VPDs) without atrioventricular or [intraventricular conduction defects](#). Upon discontinuation of [doxepin](#), progressive decrease of the VPDs were seen. Subsequent challenge with [amitriptyline](#) again resulted in VPDs which also ceased upon discontinuation of the drug. For this patient, [doxepin](#) had no advantage over [amitriptyline](#) in terms of relative [cardiotoxicity](#). A significant correlation was found between the occurrence of [premature ventricular depolarization](#) and serum levels of both antidepressants [54].

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

aJ) Since an [overdose of tricyclic antidepressants](#) has been associated with [cardiotoxicity](#), it has been assumed that tricyclic antidepressants should not be used in cardiac patients. This theory has been evaluated in a double-blind, randomized trial involving 24 depressed patients with [heart disease](#) treated with [imipramine](#), [doxepin](#), or placebo for 4 weeks [50]. Many patients were also receiving cardiac medications throughout the trial period. Patients were administered [imipramine](#) or [doxepin](#) 50 milligrams (mg) at bedtime or placebo. Doses were gradually increased every 3 days until side effects or a dose of 150 mg given at bedtime was achieved. After examination revealed that there was no evidence of cardiovascular adverse effects in patients receiving tricyclic antidepressants, dosages were allowed to be increased over 150 mg. Two patients required doses less than 50 mg/day due to severe nausea, ataxia, and sedation. As measured by radionuclide [ventriculograms](#), tricyclic antidepressants had no effect on left ventricular ejection fraction at rest or during maximal exercise. The incidence of [premature ventricular contractions](#) was reduced in patients treated with [imipramine](#); however, no consistent change was observed in patients receiving [doxepin](#) or placebo. [Imipramine](#)- and [doxepin](#)-treated patients showed a significant improvement (p less than 0.001) in depression when compared with placebo-treated patients. This study would indicate that in the absence of severe impairment of myocardial performance, depressed patients with preexisting [heart disease](#) can be treated effectively with [imipramine](#) or [doxepin](#) without an adverse effect on [ventricular rhythm](#) or hemodynamic

function. However, further evaluation of the tricyclics and their effect on cardiovascular function is required.

**b)** The literature was reviewed to ascertain the validity of suggestions that [doxepin](#) caused fewer cardiovascular effects than other antidepressants (Luchins, 1983). After reviewing the studies comparing antidepressant effects on cardiac conduction, cardiac rhythm, heart rate, blood pressure, and mechanical function of the heart, the author concluded that there is little evidence that [doxepin](#) has fewer cardiovascular effects than other antidepressants.

### 3.3.1.A.3] Edema

**a)** Incidence: 1% to 10% (topical) [44]

**b)** Edema has been reported in 1% to 10% of patients treated with [doxepin](#) cream [44].

**c)** Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause edema [42].

### 3.3.1.A.4] Electrocardiogram abnormal

**a)** Electrocardiographic changes have been reported with [doxepin](#) and manifest as increased PR interval and prolongation of QRS complex. Some studies suggest [doxepin](#) has a relatively lesser influence on intracardiac conduction than other tricyclic antidepressants [56].

**b)** Available evidence does not support the contention that [doxepin](#) is the antidepressant of choice for the treatment of depression in cardiac patients or the elderly. The incidence of [toxicity of the drug](#) in therapeutic and toxic doses appears to be similar to that of other tricyclic antidepressants. In therapeutic doses, [doxepin](#) is capable of producing prolongations of the PR, QRS, and QTc intervals, ST-T changes, [sinus tachycardia](#), [bundle branch block](#), [arrhythmias](#), orthostatic hypotension, and rarely [congestive heart failure](#). Additionally, in higher doses (overdose), the drug is capable of producing second or [third degree AV block](#), [atrial](#) or [ventricular arrhythmias](#), supine hypotension, and decreases in myocardial contractility [57]. However, therapeutic doses of [doxepin](#) in healthy adult patients are generally free of clinically important adverse cardiovascular effects, except for orthostatic hypotension [58][59][60][61]. Patients at highest risk are those with preexisting [bundle branch block](#); these patients are at greater risk of developing potentially serious conduction abnormalities during tricyclic antidepressant therapy as compared to patients with normal pretreatment EKG's [62][61].

**c)** Tricyclic antidepressants are thought to resemble [quinidine](#) with respect to certain effects on cardiac rhythm [60][61]. [Doxepin](#) may be associated with the improvement of [ventricular arrhythmias](#) when used in the treatment of depression in some patients. The efficacy of [doxepin](#) as an antiarrhythmic agent was studied in 10 cardiac patients with symptoms of frequent [ventricular premature depolarizations](#) in a dose-ranging study. Suppression of [ventricular premature depolarizations](#) (equal to or greater than 80%) was observed in 4 patients (40%) with [doxepin](#) administration; 4 of 8 patients with pairs [arrhythmia](#) and 4 of 6 with [ventricular tachycardia](#) had 90% or greater suppression. Mean maximal [doxepin](#) doses were 115 mg daily, with mean nadir total [doxepin](#) concentrations being 61 ng/mL (mean nadir total desmethyldoxepin concentrations, 51 ng/mL). Increases in heart rate and PR, QRS and QTc intervals were also observed. No significant change in resting mean left ventricular ejection fraction was observed with [doxepin](#), even in patients with moderate to severely diminished left ventricular performance. However, sedation and other side effects (dry mouth, weight gain, lightheadedness, constipation, hypotension) limited dose ranging in this study, precluding complete evaluation of the antiarrhythmic efficacy of [doxepin](#) [63]. More studies are required in larger patient populations, possibly using lower doses, to more fully evaluate antiarrhythmic effects of [doxepin](#).

**d)** In a comparison of the cardiovascular effects of [maprotiline](#) (75 to 225 mg/day) with [doxepin](#) (50 to 200 mg/day) in 49 elderly depressed patients, there were no significant differences in orthostatic



hypotension. [Maprotiline](#) caused fewer [premature ventricular contractions](#) (PVCs) and a longer PRS interval. Both drugs had a small but significant effect on heart rate and PR interval [53].

#### 3.3.1.A.5] Hypertension

a) Incidence: 3% [22]

b) [Hypertension](#) occurred in 3% of patients treated with [doxepin](#) 3 mg and less than 1% of patients receiving [doxepin](#) 6 mg, compared with 0% of placebo-treated patients in 3 clinical trials in adult patients with [chronic insomnia](#) (n=638) [22].

c) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [hypertension](#) [42].

#### 3.3.1.A.6] Hypotension

a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause hypotension [42].

b) Postural hypotension and [tachycardia](#) have been reported during [doxepin](#) therapy at an incidence of 3% to 4% [55].

c) A systematic study of the cardiovascular effects of [doxepin](#) was conducted in depressed patients with preexisting [cardiovascular disease](#). [Doxepin](#) had little effect on heart rate and did not adversely affect left ventricular function, but did have a significant antiarrhythmic effect, slowed cardiac conduction, and caused a significant increase in orthostatic hypotension. Five (16%) of the 32 patients dropped out of the study due to cardiovascular effects. The authors concluded that [doxepin](#) provided no more cardiovascular safety than [imipramine](#) or [nortriptyline](#) [52].

d) In a comparison of the cardiovascular effects of [maprotiline](#) (75 to 225 mg/day) with [doxepin](#) (50 to 200 mg/day) in 49 elderly depressed patients, there were no significant differences in orthostatic hypotension. [Maprotiline](#) caused fewer [premature ventricular contractions](#) (PVCs) and a longer PRS interval. Both drugs had a small but significant effect on heart rate and PR interval [53].

#### 3.3.1.A.7] Sudden cardiac death

a) 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 milligrams (mg) ([amitriptyline](#) or its equivalent), the rate ratio was 0.97 (95% 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 selective serotonin reuptake inhibitors was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15) [51].

#### 3.3.1.A.8] Tachycardia

a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [tachycardia](#) [42].

b) Postural hypotension and [tachycardia](#) have been reported during [doxepin](#) therapy at an incidence of 3% to 4% [55].

#### 3.3.1.A.9] Ventricular arrhythmia

a) **Ventricular arrhythmias** associated with **doxepin** and **amitriptyline** occurred in a 57-year-old man with preexisting **heart disease**. The patient was treated with a total **doxepin** dose of 250 mg/day, and after discontinuation of the cardiac medications, he developed a quadrigeminy pattern of **ventricular premature depolarizations** (VPDs) without atrioventricular or **intraventricular conduction defects**. Upon discontinuation of **doxepin**, progressive decrease of the VPDs were seen. Subsequent challenge with **amitriptyline** again resulted in VPDs which also ceased upon discontinuation of the drug. For this patient, **doxepin** had no advantage over **amitriptyline** in terms of relative **cardiotoxicity**. A significant correlation was found between the occurrence of **premature ventricular depolarization** and serum levels of both antidepressants [54].

### 3.3.2] Dermatologic Effects

#### 3.3.2.A] **Doxepin Hydrochloride**

##### 3.3.2.A.1] **Alopecia**

a) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause **alopecia** [42].

##### 3.3.2.A.2] **Contact dermatitis**

a) Severe **allergic contact dermatitis** was reported in 6 patients after they used **doxepin** 5% cream for 2 weeks to 7 months [80]. Even though dosage recommendations limit its use to 8 days, many patients use it for a much longer period. Angioedema-like swelling, **photodermatitis**, and generalized weeping **dermatitis** were some of the reactions described. All patients were patch tested to rule out a reaction to the vehicle ingredients in the cream. The authors suggest that **doxepin's histamine** blocking activity may augment **cell-mediated hypersensitivity**.

b) A 40-year-old man developed **vesicular eczema** on his arms and legs within 2 weeks of initiation of **doxepin** 5% cream for pruritic **epidermolysis bullosa pruriginosa**. The **eczema** cleared after withdrawal of **doxepin**. He had not previously used the oral form of this drug [81].

##### 3.3.2.A.3] **Eczema**

a) Incidence: topical, 1% to 10% [44]

b) **Exacerbation of eczema** has been reported in 1% to 10% of patients treated with **doxepin** cream [44].

##### 3.3.2.A.4] **Fissure in skin**

a) Incidence: topical, less than 1% [44].

b) Skin cracking and scaling has been reported in less than 1% of patients treated with **doxepin** cream [44].

##### 3.3.2.A.5] **Flushing**

a) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause flushing [42].

##### 3.3.2.A.6] **Photosensitivity**

a) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause **photosensitization** [42].

##### 3.3.2.A.7] **Pins and needles**

a) Incidence: topical, less than 1% [44].

b) Tingling has been reported in less than 1% of patients treated with **doxepin** cream [44].

**3.3.2.A.8] Pruritus**

- a) Incidence: topical, 1% to 10% [44]
- b) Exacerbation of pruritus has been reported in 1% to 10% of patients treated with doxepin cream [44].
- c) Tricyclic antidepressants, such as oral doxepin, have the potential to cause pruritus [42].

**3.3.2.A.9] Rash**

- a) Tricyclic antidepressants, such as oral doxepin, have the potential to cause skin rash [42].

**3.3.2.A.10] Sensation of burning of skin**

- a) Incidence: topical, 21% [44]
- b) The manufacturer reports that 21% of patients treated with doxepin 5% cream experienced stinging and/or burning at the site of application. Although mild in most instances, 25% of the patients who experienced this reaction categorized it as severe [44].

**3.3.2.A.11] Skin irritation**

- a) Incidence: topical, less than 1% [44].
- b) Irritation has been reported in less than 1% of patients treated with doxepin cream [44].

**3.3.2.A.12] Stretched skin**

- a) Incidence: topical, 1% to 10% [44]
- b) Tightness and dryness of skin has been reported in 1% to 10% of patients treated with doxepin cream [44].

**3.3.2.A.13] Sweating**

- a) Tricyclic antidepressants, such as oral doxepin, have the potential to cause sweating [42].

**3.3.3] Endocrine/Metabolic Effects****3.3.3.A] Doxepin Hydrochloride****3.3.3.A.1] Blood glucose level - finding**

- a) Tricyclic antidepressants, such as oral doxepin, have the potential to cause increases or decreases in blood sugar levels [42].

**3.3.3.A.2] Gynecomastia**

- a) Tricyclic antidepressants, such as oral doxepin, have the potential to cause gynecomastia in males [42].

**3.3.3.A.3] Increased body temperature**

- a) Drug fever associated with antidepressant use was reported in a 47-year-old woman with a history of major depression who was treated with a variety of antidepressants including doxepin, amitriptyline, trazodone, imipramine, maprotiline, and fluoxetine. Each time the remission of depression coincided with a low-grade fever, malaise, and sore throat. Upon discontinuation of the drug, the symptoms resolved and depression reappeared. The authors postulated this may be due to

the action of serotonin on thermoregulation and this was a particularly sensitive individual to this mechanism (Zajecka et al, 1991).

b) A **neuroleptic malignant syndrome** (NMS)-like condition occurred with the use of **lithium** and **doxepin** in a 64-year-old male with a history of depression with psychotic features. Previously, he had been successfully treated with **lithium** and **haloperidol** or **electroconvulsive therapy** (ECT); he was then treated with **lithium** 300 mg twice a day and **doxepin** 100 mg at bedtime for recurrent depression. In two weeks, he began having periods of confusion and disorientation and in another two weeks was admitted for urinary retention. His symptoms worsened after discontinuing the **lithium** and **doxepin** with gradual improvement shown on days 5 to 8. He demonstrated classic NMS symptoms in the absence of neuroleptic exposure (fever, muscle rigidity, changes in levels of consciousness, autonomic dysfunction). He later showed improvement with ECT [72].

#### **3.3.3.A.4] Syndrome of inappropriate antidiuretic hormone secretion**

a) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause **inappropriate antidiuretic hormone secretion** [42].

#### **3.3.3.A.5] Weight increased**

- a) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause weight gain [42].
- b) Weight gain has occurred during **doxepin** therapy [71].

### **3.3.4] Gastrointestinal Effects**

#### **3.3.4.A] Doxepin Hydrochloride**

##### **3.3.4.A.1] Cheilosis**

- a) Incidence: topical, 1% to 10% [44]
- b) Dry lips have been reported in 1% to 10% of patients treated with **doxepin** cream [44].

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

- a) Incidence: oral, 4% [56]
- b) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause constipation [42].
- c) Constipation has been reported to occur in approximately 4% of patients receiving therapeutic doses of **doxepin** [56].

##### **3.3.4.A.3] Dental caries**

- a) **Doxepin** has moderate anticholinergic properties which may lead to decreased salivation resulting in the development of dental caries [75][76].

##### **3.3.4.A.4] Diarrhea**

- a) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause diarrhea [42].

##### **3.3.4.A.5] Disorder of taste**

- a) Incidence: 1% to 10% [44]
- b) Changes in taste have been reported in 1% to 10% of patients treated with **doxepin** cream [44].
- c) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause taste disturbances [42].

**3.3.4.A.6] Gastroenteritis**

- a) Incidence: oral, 2% [22]
- b) **Gastroenteritis** occurred in 2% of patients treated with **doxepin** 3 mg and 0% of patients treated with **doxepin** 6 mg compared with 0% of placebo-treated patients in 3 clinical trials in adult patients with **chronic insomnia** (n=638) [22].

**3.3.4.A.7] Increased appetite**

- a) An increased appetite and craving for sweets was reported in geriatric outpatients receiving **doxepin** and other antidepressants for **depressive disorders** or other psychiatric illnesses. Of 93 patients, 34% were taking **doxepin** (average daily dose 119 mg) and this group showed the highest positive relationship to excessive appetite, craving for sweets, and weight gain [77].

**3.3.4.A.8] Increased thirst**

- a) Incidence: topical, 1% to 10% [44]
- b) Thirst has been reported in 1% to 10% of patients treated with **doxepin** cream [44].

**3.3.4.A.9] Indigestion**

- a) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause indigestion [42].

**3.3.4.A.10] Loss of appetite**

- a) Tricyclic antidepressant drugs, such as oral **doxepin**, have the potential to cause anorexia [42].

**3.3.4.A.11] Nausea**

- a) Incidence: topical, less than 1%; oral, 2% [22]
- b) Nausea occurred in 2% of patients treated with **doxepin** 3 mg and 6 mg, compared with 1% of placebo-treated patients in 3 clinical trials in adult patients with **chronic insomnia** (n=638). Nausea was one of the most common side effect reported [22].
- c) Nausea has been reported in less than 1% of patients treated with **doxepin** cream [44].
- d) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause nausea [42].
- e) Nausea and sometimes vomiting has been associated with **doxepin** [56].

**3.3.4.A.12] Stomatitis**

- a) Tricyclic antidepressants, such as oral **doxepin**, have the potential to cause **aphthous stomatitis** [42].
- b) A 34-year-old depressed, asthmatic patient was placed on **doxepin** (50 mg at bedtime) and suffered severe anticholinergic effects manifested as dry mouth, blurred vision, and constipation. During the second week of therapy, the dose was increased to 100 mg at bedtime and 5 days later the patient developed **stomatitis**. The symptoms completely resolved 4 days after discontinuation of **doxepin** [73].
- c) Approximately 7 days after beginning **ampicillin** and **doxepin** 25 mg three times/day plus 100 mg at bedtime, a 48-year-old female developed painful papular lesions on the dorsal surface of her tongue. The lesions resolved over a 3-week period following discontinuation of both medications. Because **doxepin** was relieving her depression, she began 25 mg three times/day and 50 mg at bedtime for a second time. Eight days later, generalized pain and erythema of the tongue developed and subsided over a 2-week period following **doxepin** discontinuation [74].

**3.3.4.A.13] Vomiting**

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause vomiting [42].

**3.3.4.A.14] Xerostomia**

- a) Incidence: topical, 1%; oral, 15% [44][56]  
b) Dry mouth has been reported in 1% to 10% of patients treated with [doxepin](#) cream [44].  
c) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause dry mouth [42].  
d) Dry mouth has been reported to occur in up to 15% of patients treated with [doxepin](#) [56].

**3.3.5] Hematologic Effects****3.3.5.A] Doxepin Hydrochloride****3.3.5.A.1] Agranulocytosis**

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [bone marrow depression](#) manifesting as [agranulocytosis](#) [42].  
b) Isolated cases of [anemia](#), [leukopenia](#), [lymphopenia](#), [agranulocytosis](#), and neutrophilia have occurred during [doxepin](#) therapy [48][49].

**3.3.5.A.2] Anemia**

- a) Isolated cases of [anemia](#), [leukopenia](#), [lymphopenia](#), [agranulocytosis](#), and neutrophilia have occurred during [doxepin](#) therapy [48][49].

**3.3.5.A.3] Eosinophil count raised**

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [eosinophilia](#) [42].

**3.3.5.A.4] Hemorrhage**

- a) Four patients who were receiving tricyclic antidepressants developed severe unexpected postsurgical bleeding and loss of local anesthetic effect after undergoing [nasal surgery](#). The authors suggested that this resulted from vasodilation resulting from chronic tricyclic antidepressant administration leading to increased blood supply as well as enhanced removal of cocaine from its site of action [45].

**3.3.5.A.5] Leukopenia**

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [bone marrow depression](#) manifesting as [leukopenia](#) [42].  
b) Isolated cases of [anemia](#), [leukopenia](#), [lymphopenia](#), [agranulocytosis](#), and neutrophilia have occurred during [doxepin](#) therapy [48][49].

**3.3.5.A.6] Purpura**

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [bone marrow depression](#) manifesting as [purpura](#) [42].

**3.3.5.A.7] Thrombocytopenia**

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [bone marrow depression](#) manifesting as [thrombocytopenia](#) [42].
- b) [Thrombocytopenia](#) has been reported secondary to [doxepin](#) [46]. A 73-year-old female received [doxepin](#) 75 mg daily over a period of 6 days for severe depressive reaction. On the sixth day of therapy, the patient developed [subconjunctival hemorrhages](#), generalized oozing from the mouth, and showers of [petechiae](#) over the extremities and trunk. Lab data at this time revealed [platelet](#) count 1200/cubic mm, prothrombin time 15/13 seconds, and normal PTT and Lee white clotting time. Immunoelectrophoresis was normal. [Bone marrow aspirations](#) revealed [megakaryocytic-hyperplasia](#) with many young megakaryocytes and decreased iron stores. [Doxepin](#) was discontinued and the patient was treated with [prednisone](#) 60 mg daily. The [platelet](#) count increased to 103,000/cubic mm within 3 days. [Prednisone](#) dose was tapered and the patient was started on [imipramine](#). This had no effect on [platelet](#) count and was ineffective in the treatment of her depression. [Amitriptyline](#) was started resulting in the development of [thrombocytopenia](#) which was unresponsive to [prednisone](#). [Amitriptyline](#) was discontinued and the [platelet](#) count returned to normal.
- c) [Coombs-positive hemolytic anemia](#) and [thrombocytopenia](#) with [acute renal failure](#) occurred after a patient received [doxepin](#) for approximately 5 weeks (50 to 100 mg orally daily). The patient recovered following withdrawal of [doxepin](#), [exchange transfusion](#), and repeated [hemodialysis](#). [Doxepin](#) was the only medication taken by the patient [47].

### 3.3.6] Hepatic Effects

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

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

- a) A previously well, 50-year-old man, experienced 3 separate episodes of [acute hepatitis](#) one week after taking small doses of [doxepin](#) (25 to 50 mg). Due to the patient's complete recovery between [doxepin](#) doses, the absence of other possible causes for [recurrent hepatitis](#), and the temporal relationship between [doxepin](#) dose and icteric symptoms, a causal relationship was assumed [79].
- b) Liver function tests have been reported as abnormal in several studies with [doxepin](#) [56].

##### 3.3.6.A.2] [Jaundice](#)

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [jaundice](#) [42].

### 3.3.7] Immunologic Effects

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

##### 3.3.7.A.1] [Cross sensitivity reaction](#)

- a) Two patients developed a skin rash during therapy with [desipramine](#) and [amitriptyline](#). Discontinuation of these medications in each patient resulted in subsidence of the skin rash. [Doxepin](#) was substituted in the patient receiving [desipramine](#) and [imipramine](#) was substituted in the patient receiving [amitriptyline](#). On both occasions, recurrence of the rash did not occur. These data would suggest that substitution of a structurally dissimilar antidepressant agent is a viable alternative in patients developing allergic skin reactions [84].
- b) In a double-blind, single dose, noncrossover study, 33 healthy adult volunteers (32 males, 1 female) received a single 25-mg dose of oral [desipramine](#) or [doxepin](#). The duration of H1-receptor blockade by these 2 tricyclic antidepressants, [doxepin](#) (the most potent antihistamine) and [desipramine](#) (the least potent) were compared. Results showed significant differences in the suppression of the wheal-and-flare responses to [histamine](#) between the two drugs. [Desipramine](#) suppressed the wheal for 2 days



and flare for one day, whereas [doxepin](#) suppressed the wheal for 4 days and flare for 6 days. These results suggest that [doxepin](#) should be withheld for at least 7 days before [allergy skin](#) testing [85].

### 3.3.8] Musculoskeletal Effects

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

##### 3.3.8.A.1] Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was an increased risk of nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were currently using an tricyclic antidepressant (TCA), including [amitriptyline](#), [clomipramine](#), dosulepin, [doxepin](#), [imipramine](#), [maprotiline](#), [nortriptyline](#), and opipramol, compared to those who were not exposed to antidepressants. Current TCA use was associated with an increased risk of nonvertebral fracture (hazard ratio (HR), 1.6; 95% confidence interval (CI), 1.08 to 2.38) compared with no antidepressant use. Current TCA use was also associated with an increased risk of nonvertebral fracture (HR, 1.6; 95% CI, 1.02 to 2.5) compared with past antidepressant use (n=1217). Duration of TCA use of greater than 6 months was not associated with an increased risk of fractures when compared with no antidepressant use and with past antidepressant use. Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported [82].

##### 3.3.8.A.2] Hip fracture

a) An increased incidence of hip fracture was reported in elderly patients receiving psychotropic agents. This study was a case-control evaluation of 1021 patients with hip fractures and 5606 controls. An increased risk of hip fracture was observed with the use of hypnotic/anxiolytic agents with a long elimination half-life (greater than 24 hours), tricyclic antidepressants, and antipsychotic agents. Current users were defined as subjects who had received a prescription in the 30-day period prior to the admission date for initial hospitalization. The long half-life hypnotic/anxiolytic agents studied were [lorazepam](#), [diazepam](#), [chlordiazepoxide](#), and barbiturates (excluding [phenobarbital](#)). The tricyclic antidepressants included [amitriptyline](#), [doxepin](#), and [imipramine](#); antipsychotic agents evaluated were [thioridazine](#), [haloperidol](#), [chlorpromazine](#), and perphenazine-amitriptyline. In contrast, shorter-acting hypnotic-anxiolytic agents (half-life of 24 hours or less) were not associated with an increased risk of hip fracture in these patients. The most frequently used agents in this category were [diphenhydramine](#), [hydroxyzine](#), and [chloral](#) hydrate. The increased risk of hip fracture observed in this study was directly related to the doses of the drugs. Analysis for confounding by [dementia](#) did not alter the results. Additional studies are needed to confirm these results in this and other populations and to evaluate the effects of other psychotropic drugs that have less pronounced sedative effects [83].

### 3.3.9] Neurologic Effects

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

##### 3.3.9.A.1] Asthenia

a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause weakness [42].

##### 3.3.9.A.2] Ataxia

a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause ataxia [42].

##### 3.3.9.A.3] Confusion



- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause confusion [42].

#### 3.3.9.A.4] Dizziness

- a) Incidence: topical, 1% to 10% [44]  
b) Dizziness has been reported in 1% to 10% of patients treated with [doxepin](#) cream [44].  
c) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause dizziness [42].  
d) Confusion, dizziness, disorientation, headache, fatigue, weakness, numbness, paresthesias, and ataxia have also been reported with [doxepin](#) [48].

#### 3.3.9.A.5] Extrapyramidal sign

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause extrapyramidal symptoms [42].  
b) Extrapyramidal side effects including tremor, [akathisia](#) and gait disturbances have been reported [56].  
c) Extrapyramidal symptoms were seen in 109 of 1116 patients receiving [doxepin](#) less than 75 mg to greater than 300 mg daily for periods of 4 to 52 weeks [55].  
d) A dystonic reaction occurred in a 30-year-old female who had been on antidepressant ([amitriptyline](#) 100 mg at bedtime) therapy for 3 years before discontinuing for a pregnancy. After giving birth, she took a 75-mg dose for insomnia and immediately developed dystonic symptoms. Treatment with [doxepin](#) was started and titrated up to 300 mg at bedtime. After the third 300-mg dose, she had another dystonic reaction. Later she took a single 150-mg dose for insomnia with another reaction. All symptoms resolved within 24 hours after discontinuing the medication [64].

#### 3.3.9.A.6] Headache

- a) Incidence: 1% to 10% (topical) [44]  
b) Headache has been reported in 1% to 10% of patients treated with [doxepin](#) cream [44].  
c) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause headache [42].  
d) Confusion, dizziness, disorientation, headache, fatigue, weakness, numbness, paresthesias, and ataxia have also been reported with [doxepin](#) [48].

#### 3.3.9.A.7] Myoclonus

- a) A high incidence of myoclonus during cyclic antidepressant therapy was reported with [imipramine](#), [desipramine](#), [amitriptyline](#), [doxepin](#), [trazodone](#), [nortriptyline](#), and [maprotiline](#) [66]. Ninety-eight patients with [major depression](#) (93) or [panic disorder](#) were treated with these agents in initial doses of 50 mg daily of [imipramine](#) or its equivalent increasing to a maximum of 300 mg daily after several weeks. Of these patients, 39 (40%) developed myoclonus that was clinically significant in 9 (9%) and resulted in withdrawal of the antidepressant or a medication change. Myoclonus occurred within 1 month of therapy in 81% of the 39 patients, with 46% of patients developing myoclonus within 2 weeks. The mean dose of antidepressant being administered at the time of myoclonus was 169 mg daily in [imipramine](#) equivalents, which was similar to the mean dose utilized by the patients not developing myoclonus (164 mg daily). Myoclonus was reversible upon withdrawal of the antidepressant but persisted if medication changes were not initiated; however, spontaneous remission of myoclonus was observed in 9 patients. No predictors for the development of myoclonus were observed.

#### 3.3.9.A.8] Numbness

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause numbness [42].

### 3.3.9.A.9] Paresthesia

- a) Incidence: topical, 1% to 10% [44]
- b) Paresthesia has been reported in 1% to 10% of patients treated with [doxepin](#) cream [44].
- c) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause paresthesias [42].

### 3.3.9.A.10] Seizure

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause seizures [42].
- b) A retrospective review of 47 patients treated with [doxepin](#) for anxious or [agitated depression](#) revealed a seizure disorder in 19 patients. In these 19 patients, 15 exhibited improved seizure control during therapy with [doxepin](#), while 2 exhibited no change and 2 exhibited decreased control. The authors concluded that [doxepin](#) reduced seizure frequency, and postulated 1 or a combination of 3 mechanisms: a direct antiepileptic effect; an indirect effect caused by improved affective state; or, a drug interaction with other anticonvulsants [65].
- c) Seizures are a potential complication of [doxepin](#) overdosage, but the clinical data is quite limited with few case reports. In depressed patients, [doxepin](#) produces EEG changes that are similar to other tricyclic antidepressants [56].

### 3.3.9.A.11] Somnolence

- a) Incidence: topical, 22% ; oral, 6% to 9% [44][22]
- b) Somnolence/sedation occurred in 6% and 9% of patients treated with [doxepin](#) 3 mg and 6 mg, respectively, compared with 4% of placebo-treated patients in 3 clinical trials in adult patients with [chronic insomnia](#) (n=638). Somnolence/sedation was one of the most common side effects reported [22].
- c) Drowsiness occurred in 22% of patients treated with [doxepin](#) cream compared with 2% of patients treated with placebo cream. Specifically those patients applying [doxepin](#) cream to greater than 10% of their body surface area. Alcohol consumption may exacerbate the sedative effects of [doxepin](#) cream [44].
- d) Drowsiness is the most frequently reported side effect of [doxepin](#) and appears to be dose related [68][69][70].

### 3.3.9.A.12] Tardive dyskinesia

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [tardive dyskinesia](#) [42].
- b) A prevalence study of [tardive dyskinesia](#) (TD) in the course of antidepressant therapy was conducted in 50 patients [67]. Of the 23 patients treated with [doxepin](#), 2 men receiving [doxepin](#) 100 milligrams daily developed TD. The first was a 74-year-old man suffering from a [major depressive disorder](#). He developed marked buccolingual chewing, lip smacking, and choreoathetoid movements of the body and extremities forty-five days after the start of antidepressant therapy. Seven months after the onset of TD the patient still had occasional lip smacking. The second man who developed TD was 64 years old. He had been started on [doxepin](#) 75 milligrams and increased to 100 milligrams daily after one month. Two days after the increase, chewing movements and lateral tongue movements of moderate intensity were noted without any signs of extrapyramidal symptoms. These movements persisted three months later despite a decrease in his dose to 50 milligrams daily.

### 3.3.9.A.13] Tremor

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause tremor [42].

### 3.3.10] Ophthalmic Effects

#### 3.3.10.A] Doxepin Hydrochloride

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

###### a)] General Information

1)] Pupillary dilation following administration may trigger an angle closure attack in patients with anatomically narrow angles without a patent [iridectomy](#) [43]

###### b)] Prevention and Management

1)] Consider assessing angle-closure susceptibility [43]

2)] Consider prophylactic [iridectomy](#) in susceptible patients [43]

##### 3.3.10.A.2] Blurred vision

a)] Incidence: 3% [56]

b)] Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause blurred vision [42].

c)] Blurred vision is an autonomic (anticholinergic) side effect and has been reported to occur in approximately 3% of patients receiving therapeutic doses of [doxepin](#) [56].

##### 3.3.10.A.3] Oculogyric crisis

a)] [Oculogyric crisis](#) has been reported following the use of [doxepin](#) 300 mg [64].

### 3.3.11] Otic Effects

#### 3.3.11.A] Doxepin Hydrochloride

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

a)] Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause tinnitus [42].

b)] Tinnitus has been reported during treatment of depression with [doxepin](#) in therapeutic doses in a 66-year-old female. The tinnitus recurred upon rechallenge [89].

### 3.3.12] Psychiatric Effects

#### 3.3.12.A] Doxepin Hydrochloride

##### 3.3.12.A.1] Altered mental status

a)] In a case report, [topical administration](#) of [doxepin](#) 5% cream resulted in altered mental status in a 5-year-old girl. Due to a generalized eczematous rash over approximately 50% of the body surface, the patient was prescribed [doxepin](#) 5% cream to alleviate itching. Over the course of 24 hours, 30 grams of cream was applied to the rash and the following day the patient was difficult to arouse and responded only to noxious stimuli. Physical examination revealed 3 millimeter bilaterally active pupils, a temperature of 37.2 degrees C, blood pressure of 102/62, [sinus tachycardia](#) (heart rate, 120 beats per minute), and a respiratory rate of 24 breaths per minute. Serum concentrations of [doxepin](#) and desmethyldoxepin (major active metabolite) were 11.95 nanograms per milliliter (ng/mL) and 17.71 ng/mL, respectively. Eighteen hours following skin decontamination with soap and water, a full recovery was made and the patient was discharged [87].

**3.3.12.A.2] Anxiety**

- a) Incidence: topical, less than 1% [44]
- b) Anxiety has been reported in less than 1% of patients treated with [doxepin](#) cream [44].

**3.3.12.A.3] Disorientated**

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause disorientation [42].

**3.3.12.A.4] Disturbance in thinking**

- a) Abnormal thinking and complex behaviors, such as driving, preparing and eating food, and making phone-calls while not fully awake and with amnesia of the events have occurred following ingestion of a hypnotic. These events have occurred with hypnotics at therapeutic doses, although the use of alcohol and other CNS depressants, and doses exceeding the maximum recommended amount appear to increase the risk. Use of [doxepin](#) in patients who report an episode(s) of driving while not fully awake after taking a hypnotic is strongly discouraged [22].

**3.3.12.A.5] Hallucinations**

- a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause hallucinations [42].

**3.3.12.A.6] Mood swings**

- a) Incidence: topical, 1% to 10% [44]
- b) Emotional changes have been reported in 1% to 10% of patients treated with [doxepin](#) cream [44].

**3.3.12.A.7] Suicidal thoughts****a) Adults**

1) No clinically significant differences in the risk of suicide and suicide attempts were observed across antidepressant agents and antidepressant classes in a 9-year, population-based cohort study consisting 287,543 adults. Based on the health care utilization data, the overall combined event rates of suicide death or hospitalization due to self harm ranged from 4.41 to 9.09 per 1000 person years. Among patients who received tricyclic antidepressants (TCA), including [doxepin](#) hydrochloride (n=33,410; 14,642 person-years), suicide occurred at an event rate of 0.34/1000 person-years (95% confidence interval (CI), 0.11 to 0.8) and suicide attempts occurred at a rate of 5.6/1000 person-years (95% CI, 4.45 to 6.95). Based on data among TCA users who were treatment naive (no antidepressant use in the past 3 years; n=19,658; 9277 person-years), suicide occurred at a rate of 0.32/1000 person-years (95% CI, 0.07 to 0.94) and suicide attempts occurred at a rate of 5.28/1000 person-years (95% CI, 3.91 to 6.98) among users of TCAs. Following an extensive propensity score adjustment in comparison with SSRI, TCA had an overall hazard ratio of 0.45 (95% CI, 0.19 to 1.03). Most events were reported within the first 6 months after start of therapy [86].

**b) Pediatrics**

1) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressants ([citalopram](#), [fluoxetine](#), [fluvoxamine](#), [paroxetine](#), [sertraline](#), [bupropion](#), [mirtazapine](#), [nefazodone](#), and [venlafaxine](#) extended-release) including over 4400 pediatric

patients with [major depressive disorder](#), [obsessive compulsive disorder](#), or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%, respectively). The risk of suicidality was most consistently observed in the trials that included patients with [major depressive disorder](#), but there were signs of risk emerging from trials in other psychiatric indications, such as [obsessive compulsive disorder](#) and [social anxiety disorder](#). No suicides occurred in these trials. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known [88].

#### c) Management

1) Adult and pediatric patients being treated with antidepressants for [major depressive disorder](#) who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), or mania may be at risk of [suicidal ideation](#) and behavior (suicidality). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide that is available for this drug [42][88].

#### 3.3.12.A.8] Suicide

a) No clinically significant differences in the risk of suicide and suicide attempts were observed across antidepressant agents and antidepressant classes in a 9-year, population-based cohort study consisting 287,543 adults. Based on the health care utilization data, the overall combined event rates of suicide death or hospitalization due to self harm ranged from 4.41 to 9.09 per 1000 person years. Among patients who received tricyclic antidepressants, including [doxepin](#) hydrochloride (n=33,410; 14,642 person-years), suicide occurred at an event rate of 0.34/1000 person-years (95% confidence interval (CI), 0.11 to 0.8) and suicide attempts occurred at a rate of 5.6/1000 person-years (95% CI, 4.45 to 6.95). Based on data among TCA users who were treatment naive (no antidepressant use in the past 3 years; n=19,658; 9277 person-years), suicide occurred at a rate of 0.32/1000 person-years (95% CI, 0.07 to 0.94) and suicide attempts occurred at a rate of 5.28/1000 person-years (95% CI, 3.91 to 6.98). Following an extensive propensity score adjustment in comparison with SSRI, TCA had an overall hazard ratio of 0.45 (95% CI, 0.19 to 1.03). Most events were reported within the first 6 months after start of therapy [86].

#### 3.3.13] Renal Effects

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

##### 3.3.13.A.1] [Nephrotoxicity](#)

a) [Coombs-positive hemolytic anemia](#) and [thrombocytopenia](#) with [acute renal failure](#) occurred in a patient who received [doxepin](#) for approximately 5 weeks (50 to 100 mg orally daily). The patient recovered following withdrawal of [doxepin](#), [exchange transfusion](#), and repeated [hemodialysis](#). [Doxepin](#) was the only medication taken by the patient [47].

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

a) [Urinary incontinence](#) was described as a side effect of [doxepin](#). An elderly patient received 25 mg [doxepin](#) four times a day over a period of 1 year for depression. The patient began voiding every hour and continued to have frequent [urinary tract infections](#). In addition, he commonly had an itching

rash which appeared on the thighs and buttocks. The rash did not respond to soothing lotions and [doxepin](#) was discontinued resulting in continuation of rash and disappearance of incontinence [78].

#### **3.3.13.A.3] Urinary retention**

a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause urinary retention [42].

### **3.3.14] Reproductive Effects**

#### **3.3.14.A] [Doxepin](#) Hydrochloride**

##### **3.3.14.A.1] [Galactorrhea](#)**

a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [galactorrhea](#) in females [42].

##### **3.3.14.A.2] Large breast**

a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause [breast enlargement](#) in females [42].

##### **3.3.14.A.3] Normal libido, Change in**

a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to raise or lower libido [42].

##### **3.3.14.A.4] [Priapism](#)**

a) One case of [priapism](#) is reported in a patient receiving [doxepin](#) 20 mg at bedtime. Symptoms of testicular swelling and tingling resolved upon discontinuation [90].

##### **3.3.14.A.5] Sexual dysfunction**

a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to cause testicular swelling [42].

b) Ejaculatory dysfunction has been reported in patients taking [doxepin](#), which resolves on discontinuation. Decreased libido has also been reported [90].

c) Improved sexual functioning has been noted in depressed patients with sexual dysfunction after 4 weeks of [doxepin](#) therapy in a mean dose of 122.2 mg [91].

### **3.3.15] Respiratory Effects**

#### **3.3.15.A] [Doxepin](#) Hydrochloride**

##### **3.3.15.A.1] Exacerbation of [asthma](#)**

a) Tricyclic antidepressants, such as oral [doxepin](#), have the potential to exacerbate [asthma](#) [42].

##### **3.3.15.A.2] [Upper respiratory infection](#)**

a) Incidence: oral, 2% to 4%[22]

b) [Upper respiratory tract infection/nasopharyngitis](#) occurred in 4% and 2% of patients treated with [doxepin](#) 3 mg and [doxepin](#) 6 mg, respectively, compared with 2% of placebo-treated patients in 3 clinical trials in adult patients with [chronic insomnia](#) (n=638) [22].

### **3.3.16] Other**

**3.3.16.A] Doxepin Hydrochloride****3.3.16.A.1] Adverse reaction to drug, General**

a) Doxepin therapy has been used continuously for up to 15 years in the treatment of chronic depressive illness, with maintenance of efficacy and a low order of toxicity. Continuous therapy for 5 to 15 years in 52 patients did not reveal any changes in hematologic, renal or hepatic function tests, and the drug was well tolerated in patients with concomitant cardiovascular disorders [92].

**3.3.16.A.2] Drug withdrawal**

a) Abrupt doxepin cessation following prolonged therapy has the potential to develop doxepin withdrawal symptoms [42].

**3.3.16.A.3] Fatigue**

- a) Incidence: topical, 1% to 10% [44]
- b) Fatigue has been reported in 1% to 10% of patients treated with doxepin cream [44].
- c) Tricyclic antidepressants, such as oral doxepin, have the potential to cause fatigue [42].

**3.3.16.A.4] Fever**

- a) Incidence: topical, less than 1% [44]
- b) Fever has been reported in less than 1% of patients treated with doxepin cream [44].

**3.3.16.A.5] Heart failure, Exacerbation**

See Drug Consult reference: Drugs That Cause or Exacerbate Heart Failure

**3.3.16.A.6] Hyperpyrexia**

- a) Tricyclic antidepressants, such as oral doxepin, have the potential to cause hyperpyrexia [42].

**3.3.16.A.7] Shivering**

- a) Tricyclic antidepressants, such as oral doxepin, have the potential to cause chills [42].

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

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

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

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES



**3) Crosses Placenta: Unknown****4) Clinical Management**

**a)** Although human data are limited, one case report showed poor sucking and swallowing, muscle hypotonia, drowsiness, vomiting and [jaundice](#) in a neonate following maternal use of [doxepin](#) in her third trimester and throughout the postpartum period [768]. In animal studies, there was evidence of developmental toxicity in rats and rabbits exposed to oral [doxepin](#). Therefore, [doxepin](#) should only be administered to a pregnant woman after fetal risk and maternal benefit have been assessed [22].

**5) Literature Reports**

**a)** Based on data collected through the Motherisk Program for a very small number of patients, there appear to be no differences in cognitive function, temperament, and general behavior in children exposed to [doxepin](#) throughout gestation as compared with 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 [767].

**b)** Poor sucking and swallowing, muscle hypotonia, drowsiness, vomiting, and [jaundice](#) occurred in a neonate whose mother used [doxepin](#) in her third trimester and during the postpartum period. The [doxepin](#) dose had been 75 mg/day, but was tapered in the last weeks of pregnancy and was 35 mg/day at parturition [768].

**c)** There are no adequate and well-controlled studies of [doxepin](#) use during pregnancy. In animal studies, increased rates of fetal structural abnormalities and decreased fetal body weight were reported at doses of 100 mg/kg/day or greater when pregnant rats were given oral [doxepin](#) (30, 100 and 150 mg/kg/day) during the period of organogenesis. In rats, the AUC at the no-effect dose for embryo-fetal developmental toxicity is 30 mg/kg/day (approximately 6 and 3 times the plasma AUCs for [doxepin](#) and nortriptyline at the maximum recommended human dose (MRHD)). Decreased fetal body weights in the absence of maternal toxicity were reported when oral [doxepin](#) doses of 60 mg/kg/day were given to pregnant rabbits during the period of organogenesis. In rabbits, the AUC at the no-effect dose for embryo-fetal developmental toxicity is 30 mg/kg/day (approximately 6 and 18 times the plasma AUCs for [doxepin](#) and nortriptyline at the MRHD). Reduced pup survival and transient growth delay were observed when rats were given oral [doxepin](#) 100 mg/kg/day during pregnancy and lactation periods. In this rat study, the AUC at the no-effect dose for embryo-fetal developmental toxicity is 30 mg/kg/day (approximately 3 and 2 times the plasma AUCs for [doxepin](#) and nortriptyline at the MRHD) [22].

**B) Breastfeeding**

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

**2)** Micromedex Lactation Rating: Infant risk has been demonstrated.

**a)** Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue breastfeeding.



### 3) Clinical Management

a) Both [doxepin](#) and its active metabolite have been found in breast milk, and the active metabolite has been found in infant serum at a concentration similar to therapeutic concentrations in adults [770]. Sedation and [respiratory depression](#) have been reported in a breastfeeding infant [771]. Therefore, caution should be used when administering [doxepin](#) to a nursing mother [22]. Alternatively, available data suggest that [clomipramine](#) is a safer agent for use during breastfeeding, and [clomipramine](#) is considered compatible with breastfeeding by the American Academy of Pediatrics.

### 4) Literature Reports

a) [Doxepin](#) and desmethyldoxepin levels were measured in the milk of a mother being treated with [doxepin](#) 150 mg daily for [major depressive disorder](#). The milk to plasma ratio averaged 1.46 for both [doxepin](#) and desmethyldoxepin. With an average maternal serum level of 46 mcg/L for [doxepin](#) and 90 mcg/L for desmethyldoxepin, a nursing infant would consume a dose of 237 mcg in 1.2 L of milk per day [770].

b) [Respiratory depression](#) occurred in an 8-week-old breastfed girl whose mother was receiving [doxepin](#) 25 mg 3 times daily. In the infant's serum, the level of [doxepin](#) was almost undetectable (3 mcg/mL); therefore, the [respiratory depression](#) was attributed to the high concentrations of N-desmethyldoxepin (58 and 66 mcg/mL) which were similar to the levels in the mother. After discontinuing breastfeeding, the infant's respiration normalized within 24 hours [771].

c) Poor sucking and swallowing, muscle hypotonia, drowsiness, vomiting, and [jaundice](#) occurred in a neonate whose mother used [doxepin](#) in her third trimester and during the postpartum period. The [doxepin](#) dose had been 75 mg/day, but was tapered in the last weeks of pregnancy and was 35 mg/day at parturition. The amount of [doxepin](#) and desmethyldoxepin (active metabolite) ingested by the nursing infant was estimated at 10 to 20 mcg/kg/day (2.5% of the weight-adjusted dose of the mother) [772].

### 5) Drug Levels in Breastmilk

#### a) [Doxepin](#) Hydrochloride

##### 1) Parent Drug

##### a) Milk to Maternal Plasma Ratio

1) 1.08 to 1.66 [770]

##### 2) Active Metabolites

##### a) Desmethyldoxepin [783]

1) Milk to Maternal Plasma Ratio

a) 1.02 to 1.53 [770]

### 3.5] Drug Interactions

#### 3.5.1] Drug-Drug Combinations

##### 3.5.1.A] Abiraterone

- 1) Interaction Effect: increased plasma concentrations of CYP2D6 substrate
- 2) Summary: Coadministration of abiraterone (a CYP2D6 inhibitor) with a CYP2D6 substrate may result in increased plasma concentrations of the CYP2D6 substrate. When abiraterone (1000 mg/day) and [prednisone](#) (5 mg twice daily) were coadministered with the CYP2D6 substrate [dextromethorphan](#) (30 mg), the [dextromethorphan](#) C<sub>max</sub> and AUC were increased 2.8-fold and 2.9-fold, respectively. If an alternative to the CYP2D6 substrate cannot be used, use caution and consider reducing the dose of the CYP2D6 substrate as necessary during coadministration[179].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of abiraterone, a CYP2D6 inhibitor, with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. If an alternative to the CYP2D6 substrate cannot be used, use caution and consider a dose reduction of the CYP2D6 substrate as indicated during coadministration[179].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by abiraterone

##### 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[246], [amiodarone](#) [247], [azimilide](#) [248], [bretylium](#) [249], [ibutilide](#) [250], [sotalol](#) [253], [dofetilide](#) [252], and [sotalol](#) [253]. 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 [254][255].
- 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 [244].

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 [245].

### 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[533]. 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](#)[533]. 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 [533].

### 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[533]. 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](#)[533]. 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 [533].

**3.5.1.E] Acenocoumarol**

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[566][567]. Considerable interindividual differences may be found [568].
- 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 [563]. 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 [564]. 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 [565]. 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[230]. 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[230]. If concomitant administration is required, monitor the patient closely.
- 7) Probable Mechanism: potentiation of vascular effects of [albuterol](#)

**3.5.1.G] Almotriptan**

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [doxepin](#)[22] 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 is recommended [180]. 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 [99].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [almotriptan](#) and [doxepin](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, monitoring of patient for neurologic changes and gastrointestinal symptoms during treatment is recommended[180].
- 7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.H] Amifampridine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#)[598].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#)[598].
- 7) Probable Mechanism: additive QT-interval prolongation

#### 3.5.1.I] Amiodarone

- 1) Interaction Effect: increased risk of QT prolongation and [torsades de pointes](#)
- 2) Summary: Avoid the concomitant administration of [amiodarone](#) and a QT prolonging agent since it may result in additive effects on the QT interval and increase the risk of [torsades de pointes](#). Due to the long half-life of [amiodarone](#), this interaction is possible even after the discontinuation of [amiodarone](#)[390].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the concomitant administration of [amiodarone](#) and a QT prolonging agent since it may result in additive effects on the QT interval and increase the risk of [torsades de pointes](#). Due to the long half-life of [amiodarone](#), this interaction is possible even after the discontinuation of [amiodarone](#)[390].
- 7) Probable Mechanism: additive effects on QT interval

#### 3.5.1.J] Amisulpride

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

2) Summary: Use caution with the concomitant use of amisulpride with other agents that prolong the QT interval and monitor the patient's heart rhythm prior to coadministration. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such as [torsade de pointes](#)[169].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the concomitant use of amisulpride with other agents that prolong the QT interval and monitor the patient's heart rhythm prior to coadministration. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such [torsade de pointes](#)[169].

7) Probable Mechanism: additive QT prolongation

### 3.5.1.K] Amitriptyline

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

2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor[662], and [doxepin](#) [218] 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 [99].

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](#)[662]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.L] 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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.M] [Amoxapine](#)

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

2) Summary: Both [amoxapine](#)[137] and [doxepin](#) 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](#). 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 [99]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amoxapine](#) and [doxepin](#) are used concurrently.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [amoxapine](#) and [doxepin](#), as it 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 effect

### 3.5.1.N] [Amphetamine](#)

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

2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[663].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally,



coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[663].

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

### 3.5.1.O] [Amprenavir](#)

1J) Interaction Effect: increased tricyclic agent serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))

2J) 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](#)[500].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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](#))[500].

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

### 3.5.1.P] [Amitolmetin Guacil](#)

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[533]. 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](#)[533]. 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 [533].



**3.5.1.Q| 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](#)[480].
- 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](#)[480].
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.R| Anisindione**

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[367][368]. Considerable interindividual differences may be found [369].
- 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 [364]. 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 [365]. 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 [366]. 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.S| 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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.T] [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[529].

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.U] [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[525]. 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[525].

7J) Probable Mechanism: potentiation of cardiovascular effects

### 3.5.1.V] Aripiprazole

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

2J) Summary: Aripiprazole has been associated with QTc interval prolongation[746], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Aripiprazole has been associated with QTc interval prolongation[746], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.

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

### 3.5.1.W] Arsenic Trioxide

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 arsenic trioxide. Possible pharmacodynamic interactions can occur between arsenic trioxide and potentially arrhythmogenic agents such as tricyclic antidepressants that prolong the QT interval[639]. 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 [640][641].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

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

7J) Probable Mechanism: additive effects on QT prolongation

8J) Literature Reports

aJ) 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 [636][637].

bJ) 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 [638].

**3.5.1.X] 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[533]. 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](#)[533]. 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 [533].

**3.5.1.Y] 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[644][645].
- 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 [643]. [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.Z] Azimilide**

- 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[246], [amiodarone](#) [247], azimilide [248], [bretylium](#) [249], [ibutilide](#) [250], sematilide [251], [dofetilide](#) [252], and [sotalol](#) [253]. 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 [254][255].

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 [244].

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 [245].

### 3.5.1.AA] [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](#)[413]. In addition, concomitant [imipramine](#) and [baclofen](#) may result in additive muscle relaxant effects [414].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

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 [411].

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 [412].

### 3.5.1.AB] 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[161]. 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.AC] 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[161]. 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.AD] Benzphetamine

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[663].



- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[663].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

### 3.5.1.AE] [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[755], 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[755], as coadministration may increase the risk of [ventricular arrhythmias](#).
- 7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.AF] [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. The interaction with [doxepin](#) is dose related[213][214]; [doxepin](#) in doses less than 150 mg daily may be used with bethanidine, but the antidepressant effect may be insufficient at such a low dose [215][216][217].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: The combination of bethanidine and [doxepin](#), as well as other tricyclic antidepressant agents, should be avoided. An alternative antihypertensive should be considered.
- 7) Probable Mechanism: decreased uptake of bethanidine into adrenergic neurons
- 8) Literature Reports

- a) Adequate control of [hypertension](#) was reported in only two of eight adult hypertensive patients who received bethanidine or debrisoquine concurrently with a tricyclic antidepressant. In 24 control patients given the same drugs without antidepressants, blood pressure control was achieved in 18. Withdrawal of hypotension that necessitated a reduction in dosage of bethanidine or debrisoquine [212].

### 3.5.1.AG] [Bretylum](#)

- 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[246], [amiodarone](#) [247], azimilide [248], [bretylium](#) [249], [ibutilide](#) [250], sotalol [251], [dofetilide](#) [252], and [sotalol](#) [253]. 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 [254][255].

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 [244].

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 [245].

### 3.5.1.AH] [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.AI] [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[98].



- 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[98].
- 7) Probable Mechanism: additive extrapyramidal side effects

### 3.5.1.AJ] Bufexamac

- 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.AK] Buprenorphine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Exercise caution with the concomitant use of [buprenorphine](#) and other agents that affect the serotonergic neurotransmitter system due to the potential of [serotonin syndrome](#). If concurrent use is required, monitor for [serotonin syndrome](#), particularly during treatment initiation and with dosage adjustments[385]
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [buprenorphine](#) with other agents that affect the serotonergic neurotransmitter system should be undertaken with caution due to the potential of [serotonin syndrome](#). If concurrent use is required, monitor for [serotonin syndrome](#), particularly during treatment initiation and with dosage adjustments[385]
- 7) Probable Mechanism: additive serotonergic effects

### 3.5.1.AL] 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[171].

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[171].

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 [172].

b)) Coadministration of **buPROPion** 150 mg twice daily and a single dose of **desipramine** 50 mg (a CYP2D6 substrate) in healthy volunteers who were extensive CYP2D6 metabolizers (n=15) resulted in a 2-fold and 5-fold increase in **desipramine** C<sub>max</sub> and AUC respectively. The effect persisted for 7 days following the last dose of **buPROPion** [173].

### 3.5.1.AM] 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[672][673][674]. 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[672][673][674].

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AN] 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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.AO] 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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.AP] Cannabis**

**1)** Interaction Effect: **tachycardia** and **delirium**

**2)** Summary: Concomitant tetrahydrocannabinol and tricyclic antidepressant therapy has increased the heart rate and cause **delirium** beyond that expected with either drug alone[430][431].

**3)** Severity: moderate

**4)** Onset: rapid

**5)** Substantiation: probable

**6)** Clinical Management: Caution is advised if patients use cannabis with a tricyclic antidepressant. Monitor heart rate changes closely.

**7)** Probable Mechanism: possibly due to beta-adrenergic effect of cannabis coupled with the anticholinergic effect of tricyclic antidepressants

**8) Literature Reports**

**a)** A 21-year-old female receiving oral **nortriptyline** 30 milligrams at bedtime for 9 months developed marked **sinus tachycardia** (160 beats/minute) within 30 minutes of smoking a cannabis cigarette. The patient's heart rate was about 90 beats/minute before smoking the cannabis. She had used cannabis many times before starting the **nortriptyline** without ill effects [428].

**b)** Four cases of **tachycardia**, cognitive changes, and **delirium** have been reported in adolescent males treated with tricyclic antidepressants who smoked marijuana. One of the four cases was evaluated by a physician, the others were later accounts of the event. The toxic effects were considered by the reporters to have resulted from a drug interaction because they occurred with lower doses of marijuana than are common in other reports of marijuana toxicity (usually greater than 20 mg). In case 1, a 16-year-old male taking **nortriptyline** 75 mg/day presented with **tachycardia** (130 beats/minute), **delirium**, confusion, and **short-term memory loss** 30 minutes after smoking one marijuana cigarette. Symptoms resolved spontaneously after 24 hours. In case 2, an 18-year-old male taking **desipramine** 200 mg/day presented 12 hours after smoking marijuana with symptoms of edginess, severe dry mouth, lightheadedness, confusion, short-term **memory impairment**, and **tachycardia** (110 beats/minute). Symptoms resolved within 48 hours. Case 3, a 15-year-old male taking **desipramine** 150 mg/day and **sertraline** 50 mg/day, reported mood lability, irritability, and a racing heart after smoking 2 marijuana cigarettes which resolved after 16 hours. Case 4, a 16-year-old male taking **desipramine** and **clonidine** reported hallucinations, confusion, mild shortness of breath, and elevated heart rate after smoking marijuana. This was different than the effect he experienced prior to taking **desipramine** [429].

**3.5.1.AQ] Carbamazepine**

- 1) Interaction Effect: decreased [doxepin](#) effectiveness and possibly increased [carbamazepine](#) toxicity ([diplopia](#), blurred vision, dizziness, tremor)
- 2) Summary: The concomitant use of [carbamazepine](#) and antidepressants has been reported to decrease [doxepin](#) levels[136].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for clinical efficacy of the [doxepin](#) 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 [doxepin](#) metabolism
- 8) Literature Reports

a) The effect of [carbamazepine](#) on [doxepin](#) levels were examined in 17 psychiatric inpatients who were stabilized for a minimum of 7 days prior to measurement of baseline antidepressant concentrations. The average daily [doxepin](#) dosage was 201.5 mg. [Carbamazepine](#) was added in a mean dose of 593 mg and continued over a 4-week period. Serum [doxepin](#) concentrations were decreased to 46% in patients receiving combination therapy compared to patients receiving [doxepin](#) alone [135].

### 3.5.1.AR] [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.AS] [Chloroquine](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) 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[167][168].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.AT] [Chlorotrianisene](#)

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[722], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [723]. The effects of the interaction appear to be estrogen dose-related [724] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [725].

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) 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 [713].

b) A case reported demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 mg and [imipramine](#) 100 mg [714]. 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 [715].

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 [716].

d) The effects of oral contraceptives on [clomipramine](#) were 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 [717].

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 [718].

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 [719].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [720]. 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 [721].

### 3.5.1.AU] [Choline 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.AV] [Cimetidine](#)

- 1) Interaction Effect: [doxepin](#) toxicity (dry mouth, blurred vision, urinary retention)
- 2) Summary: Concomitant administration of [doxepin](#) 50 mg daily and [cimetidine](#) 600 mg twice daily was reported to result in significant increases in [doxepin](#) concentration and elimination half-life[554][555][556].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor serum tricyclic antidepressant levels within the first few days of starting or discontinuing [cimetidine](#). An H2 blocker that does not impair the metabolism of the tricyclic agents, such as [ranitidine](#) or [famotidine](#), may be an alternative.
- 7) Probable Mechanism: decreased [doxepin](#) metabolism

### 3.5.1.AW] [Cinacalcet](#)

- 1) Interaction Effect: increased [doxepin](#) plasma concentrations
- 2) Summary: [Cinacalcet](#) is partially metabolized by and is a strong inhibitor of the CYP2D6 isozyme. [Cinacalcet](#) may increase blood concentrations of drugs that are predominantly metabolized by CYP2D6 and have a narrow therapeutic index, such as certain tricyclic antidepressants. Therefore, if [cinacalcet](#) and [doxepin](#) are coadministered, dose adjustments of [doxepin](#) may be required[219]. Monitoring of [doxepin](#) plasma concentrations is recommended during the concomitant use of [doxepin](#) with a CYP2D6 inhibitor, such as [cinacalcet](#). Dose adjustments of one or both drugs, especially during therapy initiation and discontinuation, may be warranted [218].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: If [cinacalcet](#) is coadministered with a tricyclic antidepressant (TCA), such as [doxepin](#)[218], a dose reduction of the TCA may be necessary [219]. [Doxepin](#) plasma concentrations should be closely monitored when [doxepin](#) and [cinacalcet](#) are used concurrently [218].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [doxepin](#) metabolism by [cinacalcet](#)

### 3.5.1.AX] [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](#)[152].
- 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](#)[152].
- 7)) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.AY] [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[667].
- 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[667].
- 7)) Probable Mechanism: additive prolongation effects on QT interval

### 3.5.1.AZ] [Clonidine](#)

- 1)) Interaction Effect: decreased antihypertensive effectiveness
- 2)) Summary: Concomitant [clonidine](#) and tricyclic antidepressant (TCA) therapy may impair the antihypertensive effects of [clonidine](#)[627]. 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 [628][629][630][631]. Mianserin, a tetracyclic antidepressant, was not shown to exhibit the impairment of [clonidine's](#) antihypertensive effects seen with tricyclic antidepressants [632][633].
- 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)) The interaction between [clonidine](#) and [desipramine](#) was 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 [624].

b)) Eleven drug-free patients who met the Research Diagnostic Criteria for [Major Depressive Disorder](#) enrolled 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 [625].

c) 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 [626].

### 3.5.1.BA] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.BB] 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](#)[463][464][465][466]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [467]. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#), and monitor patients closely [468][469].
- 3) Severity: major
- 4) Onset: delayed

**5j) Substantiation: theoretical**

**6j) Clinical Management:** Concomitant use of a tricyclic antidepressant, such as [doxepin](#), and a monoamine oxidase inhibitor (MAOI), such as clorgyline, should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#). If [doxepin](#) is replacing treatment with clorgyline, a minimum of 14 days should elapse after clorgyline is discontinued before [doxepin](#) therapy begins[257]. There is no specific washout period for replacing [doxepin](#) treatment with clorgyline. However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with the MAOI [103].

**7j) Probable Mechanism: altered catecholamine uptake and metabolism****8j) Literature Reports**

**aj)** 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 [445][446][447][448][449][450]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [451].

**bj)** Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). 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 [452].

**cj)** A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching 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 [453].

**dj)** 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 [454].

**ej)** 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 [455].

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 [456].

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 [457] [447][448][458][459]. 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 [460]. 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 [460]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [461][448][462].

### 3.5.1.BC] [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[156]. 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[156]. 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 [157].

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 [158].

### 3.5.1.BD] 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[685], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [686]. The effects of the interaction appear to be estrogen dose-related [687] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [688].

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 [676].

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 [677] [678].

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 [679].

**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 [680].

**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 [681].

**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 [682].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [683]. 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 [684].

### 3.5.1.BE] 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[363]. 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[363]. Dose reduction of crizotinib may be warranted.

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



**3.5.1.BF] 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[531][532].
- 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[531][532].
- 7) Probable Mechanism: additive serotonergic effects

**3.5.1.BG] 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[433]. 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[433]. Exercise caution with concomitant use and consider assessment and periodic monitoring for [ventricular arrhythmia](#).
- 7) Probable Mechanism: additive QT prolongation

**3.5.1.BH] 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[176][177].
- 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[176][177].

7) Probable Mechanism: unknown

### 3.5.1.BI] 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[672][673][674]. 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[672][673][674].

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BJ] 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[619].

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[619].

7) Probable Mechanism: additive QT- interval prolongation

### 3.5.1.BK] 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[672][673][674]. 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[672][673][674].

7) Probable Mechanism: additive effects on the QT interval



### 3.5.1.BL] Desogestrel

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic antidepressant toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].
- 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
- 8) Literature Reports

a) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

**d)** The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

**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 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 [354].

**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 [355].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.BM] 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[432].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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[432].

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

8J) Literature Reports

aJ) Coadministration of [desipramine](#) (a CYP2D6 substrate) 50 mg with desvenlafaxine 400 mg/day (unapproved dosing) in a clinical study resulted in an increase of approximately 50% for the C<sub>max</sub> 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<sub>max</sub> and 17% in AUC) [432].

### 3.5.1.BN] Dexibuprofen

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[533]. 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](#)[533]. 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 [533].

### 3.5.1.BO] Dexketoprofen

- 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.BP] [Dextroamphetamine](#)

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[663].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[663].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

### 3.5.1.BQ] [Dextromethorphan](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: The concomitant use of [dextromethorphan](#) and a tricyclic antidepressant (such as [doxepin](#)) may result in an increased risk of [serotonin syndrome](#). While not specifically studied with [doxepin](#), 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[692]. If both [doxepin](#) 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 [doxepin](#)), as concomitant use may result in an increased risk of [serotonin syndrome](#)[692].

7) Probable Mechanism: additive CNS serotonin concentrations

### 3.5.1.BR] [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[533]. 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](#)[533]. 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 [533].

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

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[608][609]. Considerable interindividual differences may be found [610].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In patients receiving oral [anticoagulant therapy](#), the prothrombin time ratio or [international normalized ratio](#) (INR) should be closely monitored with the addition and withdrawal of treatment with [doxepin](#), 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 [605]. 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 [606]. 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 [607]. 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.BT] [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[424], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [425]. The effects of the interaction appear to be estrogen dose-related [426] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [427].

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)) Some studies 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 [415].



b)) A case reported by [416] 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 [417].

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 [418].

d)) The effect of oral contraceptives on [clomipramine](#) was studied 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 [419].

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 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 [420].

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 [421].

g)) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [422]. 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 [423].

### 3.5.1.BU] Dienogest

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic antidepressant toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].
- 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
- 8) Literature Reports

a) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

**d)** The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

**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 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 [354].

**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 [355].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.BV] [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[407], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [408]. The effects of the interaction appear to be estrogen dose-related [409] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [410].

**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.

**7j) Probable Mechanism:** possible estrogen-enhanced hepatic metabolism of the tricyclic**8j) 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 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 [398].

**b)** A case reported by [399] 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 [400].

**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 [401].

**d)** The effect of oral contraceptives on [clomipramine](#) was studied 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 [402].

**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 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 [403].

**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 [404].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [405]. 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 [406].

### 3.5.1.BW] [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.BX] [Dipyrrone](#)

**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[533]. 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](#)[533]. 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 [533].

### 3.5.1.BY] [Disopyramide](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Concomitant use of tricyclic antidepressants, including [doxepin](#), and class IA antiarrhythmics, including [disopyramide](#), may increase the risk of [cardiotoxicity](#) due to similar cardiac effects of these drugs[209][210]. Therefore, monitoring the patient for signs and symptoms of [cardiac toxicity](#) during coadministration of [disopyramide](#) and [doxepin](#) may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [disopyramide](#) and [doxepin](#) may increase the risk of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs[209][210]. 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) 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](#) [211].

### 3.5.1.BZ] [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[246], [amiodarone](#) [247], azimilide [248], [bretylium](#) [249], [ibutilide](#) [250], sotalol [251], [dofetilide](#) [252], and [sotalol](#) [253]. 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 [254][255].

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 [244].

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 [245].

### 3.5.1.CA] [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[150][151].

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[150][151].

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

### 3.5.1.CB] [Domperidone](#)

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

2)) Summary: Use caution with coadministration of [doxepin](#), a potential QT interval prolonging drug, and domperidone, a drug that has been associated with an increased risk of sudden cardiac death. In case control studies, an increased risk of sudden cardiac death was observed with the use of oral domperidone, particularly at doses greater than 30 mg/day and in patients older than 60 years. If coadministration

is necessary, initiate domperidone at the lowest possible dose and titrate with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure[559].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when coadministering domperidone and [doxepin](#) as it may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#) and sudden cardiac death, particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years. If coadministration is necessary, initiate domperidone at the lowest possible dose and titrate with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure[559].

7) Probable Mechanism: additive effects on the QT interval

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

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

2) Summary: [Donepezil](#) has been associated with QT-interval prolongation[284][285]. 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[284][285]. Use caution when administering [donepezil](#) concomitantly with other drugs that cause QT-interval prolongation

7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.CD] [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](#)[612].

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](#)[612].

7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.CE] [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[689][690].

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.CF] [Drospirenone](#)

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].

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

8) Literature Reports

a) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

**d)** The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

**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 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 [354].

**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 [355].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.CG| 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[533]. 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](#)[533]. 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 [533].

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

1J) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))

2J) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[153].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[153]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).

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

### 3.5.1.CIJ [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<sub>max</sub> in patients with the CYP2B6 \*6/\*6 genotype was 2.25-fold higher than the mean C<sub>max</sub> 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[370].

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[370].

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<sub>max</sub> in subjects with the CYP2B6

\*6/\*6 genotype was 2.25-fold higher than the mean C<sub>max</sub> 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 [370].

### 3.5.1.CJ] Eliglustat

- 1) Interaction Effect: increased CYP2D6 substrate exposure
- 2) Summary: Use caution with coadministration of eliglustat, a CYP2D6 inhibitor, with CYP2D6 substrates, as concurrent use may increase serum concentrations of CYP2D6 substrates. Among patients with [Gaucher disease type 1](#), concurrent use of eliglustat increased mean C<sub>max</sub> and AUC of [metoprolol](#) (a CYP2D6 substrate) from 1.2- to 1.7-fold in intermediate CYP2D6 metabolizers and 1.6- to 2.3-fold higher than baseline in extensive CYP2D6 metabolizers, respectively. If concurrent use is necessary, monitor therapeutic drug concentrations as clinically indicated, or consider reducing the dose of the CYP2D6 substrate and titrating to clinical effect[494].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of eliglustat with CYP2D6 substrates, as concurrent use may increase serum concentrations of CYP2D6 substrates. If concurrent use is necessary, monitor therapeutic drug concentrations as clinically indicated, or consider reducing the dose of the CYP2D6 substrate and titrating to clinical effect[494].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by eliglustat
- 8) Literature Reports

a) Among patients with [Gaucher disease type 1](#) who were extensive CYP2D6 metabolizers, mean C<sub>max</sub> and AUC of [metoprolol](#) (a CYP2D6 substrate) increased by 1.7- and 2.3-fold over baseline, respectively, when used concurrently with eliglustat 127 mg twice daily (unapproved dose) and by 1.2- and 1.6-fold, respectively, in intermediate CYP2D6 metabolizers [494].

### 3.5.1.CK] Enflurane

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)) and an increased risk of seizure activity
- 2) Summary: [Enflurane](#) may prolong the QT interval in some patients[748]. 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 [749]. Concomitant administration of [amitriptyline](#) and [enflurane anesthesia](#) has been reported to result in seizures in two cases [750].
- 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 [747]. 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.CL] [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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512] 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 [515][516][517][518].
- 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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512]. 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 [513].

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 [514].

### 3.5.1.CM] [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[616]. [Erythromycin](#) has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval [617]. Tricyclic antidepressants have been shown to prolong the QTc

interval at the recommended therapeutic dose [618]. 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](#) [613].

b) Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose [614].

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 [615].

### 3.5.1.CN] Escitalopram

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

2) Summary: Escitalopram is a QT-interval-prolonging drug[471]. 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[471]. 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.CO] 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[648]. 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[648]. If coadministering, use caution and monitor the patient closely.
- 7) Probable Mechanism: inhibition of CYP2C19-mediated metabolism by eslicarbazepine acetate

### 3.5.1.CP| 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[685], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [686]. The effects of the interaction appear to be estrogen dose-related [687] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [688].
- 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 [676].

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 [677] [678].



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 [679].

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 [680].

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 [681].

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 [682].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [683]. 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 [684].

### 3.5.1.CQ] [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[685], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [686]. The effects of the interaction appear to be estrogen dose-related [687] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [688].

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 [676].

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 [677] [678].

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 [679].

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 [680].

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 [681].

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 [682].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [683]. 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 [684].

### 3.5.1.CR| [Estradiol Cypionate](#)

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].

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

8) Literature Reports

a) Some studies 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 [349].

**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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

**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 [352].

**d)** The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

**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 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 [354].

**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 [355].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.CS] **Estradiol Valerate**

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on **estrogen therapy** [361].

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

8) Literature Reports

a) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

**d)** The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

**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 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 [354].

**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 [355].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.CT] 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 [685], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [686]. The effects of the interaction appear to be estrogen dose-related [687] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [688].

**3)** Severity: minor

**4)** Onset: delayed

**5)** 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 [676].

**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 [677] [678].

**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 [679].

**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 [680].

**ej)** 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 [681].

**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 [682].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [683]. 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 [684].

### 3.5.1.CU] [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[685], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [686]. The effects of the interaction appear to be estrogen dose-related [687] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [688].

**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 [676].

**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 [677] [678].

**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 [679].

**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 [680].

**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 [681].

**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 [682].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [683]. 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 [684].

**3.5.1.CV] 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[685], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [686]. The effects of the interaction appear to be estrogen dose-related [687] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [688].

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 [676].

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 [677] [678].

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 [679].

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 [680].

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 [681].

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 [682].

g)) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [683]. 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 [684].

### 3.5.1.CW] 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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.CX] **Ethinyl Estradiol**

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

2)) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on **estrogen therapy** [361].

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

8)) Literature Reports

a)) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

d) The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

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 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 [354].

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 [355].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.CY] [Ethinodiol Diacetate](#)

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



2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].

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

8) Literature Reports

a) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

d)) The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

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 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 [354].

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 [355].

g)) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.CZ] 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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512] 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 [515][516][517][518].

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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.



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

8J) Literature Reports

aJ) 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 [513].

bJ) 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 [514].

### 3.5.1.DA| [Etodolac](#)

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[533]. 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](#)[533]. 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 [533].

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

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[533]. 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

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](#)[533]. 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 [533].

### 3.5.1.DC] [Etonogestrel](#)

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].

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

8) Literature Reports

a) Some studies 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 [349].

**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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

**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 [352].

**d))** The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

**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 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 [354].

**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 [355].

**g))** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

**3.5.1.DD] 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[533]. 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](#)[533]. 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 [533].

**3.5.1.DE] 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[533]. 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](#)[533]. 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 [533].

**3.5.1.DF] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.DG| [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[170], including SSRIs [665][664][666]. [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 [170]. 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 [99].
- 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](#)) [170]. 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 [99].
- 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 **cycloheptadine**. After 3 days, the patient's temperature and CPK level normalized and she later extubated with no further complications [664].

b) **Serotonin syndrome** following the administration of IV **fentanyl** during surgical procedures was reported in 2 patients also taking SSRIs (**sertraline** and escitalopram). The first patient received IV **fentanyl** (50 micrograms), **midazolam** (2 mg), and 2 doses **propofol** (60 mg and 40 mg) in an **outpatient surgery** center prior to a **carpal tunnel release** procedure. Postoperatively the patient began shivering and became increasingly agitated for which she was transferred to the emergency department. On presentation the patient was combative, diaphoretic, confused, was unable to follow commands, tachycardic, hypertensive, had hyperreflexia, and ankle clonus. Baseline **creatinine** kinase rose to 613 units/L on day 2 of hospitalization. The toxicology service treated her with escalating doses of benzodiazepines with no improvement. The patient was subsequently intubated and sedated with a continuous **propofol** infusion. After 2 days the patient was extubated and by day 3 all symptoms had resolved and the patient was discharged home. The second patient was a 59-year-old woman admitted for an **omentectomy** for which she received IV **fentanyl** 250 micrograms, **etomidate**, vecuronium, **morphine** and cephazolin. Following **extubation** the patient became hypoxic and acidotic and was reintubated and transferred to the ICU. On postoperative day 1 she was extubated and later became tachycardic and was unable to follow commands. On examination the patient was agitated and diaphoretic, had patellar hyperreflexia and a bilateral 3 to 4 beat ankle clonus. Laboratory evaluation was remarkable for a peak **creatinine kinase** of 1161 units/L on postoperative day 2. The patient was treated with **lorazepam** and **cycloheptadine** with resolution of symptoms after 3 days [665].

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 [666].

### 3.5.1.DH] 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[533]. 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[533]. 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 [533].

### 3.5.1.DI] 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[533]. 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[533]. 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 [533].

### 3.5.1.DJ] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.DK] Fluconazole

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Case reports have described QT prolongation and torsades de points associated with [fluconazole](#)[164]. Several tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose [165]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [fluconazole](#) and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.DL] Flufenamic 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.DM] [Fluoxetine](#)

- 1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)
- 2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[650]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [651][657][658][659][660][661]. 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 [650].
- 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[650]
- 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 [650].

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 [651].

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 [652].

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 [653].

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) [654].

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 [655].

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 [656].

### 3.5.1.DN] [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.DO| [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[524]. 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[524].

7) Probable Mechanism: potentiation of cardiovascular effects

### 3.5.1.DP| [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](#)[500].

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](#))[500].

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

### 3.5.1.DQ| [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[693][694].
- 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.DR| [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](#). 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[181][182].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor therapeutic efficacy of [doxepin](#); 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.DS| [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.[100]. 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 [99]. Therefore, if [serotonin syndrome](#) is suspected, discontinue use of [frovatriptan](#) [100]. Alternatively, if [serotonin syndrome](#) develops, discontinue both offending agents ([frovatriptan](#) and the tricyclic antidepressant) and provide supportive care and other therapy as necessary [99].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [frovatriptan](#) and a tricyclic antidepressant[99], 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](#) [100]. Alternatively, if [serotonin syndrome](#) develops, discontinue both offending agents ([frovatriptan](#) and the tricyclic antidepressant) and provide supportive care and other therapy as necessary [99].

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

### 3.5.1.DT] [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[646].

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.DU] [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[622].

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.DV] [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[672][673][674]. 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[672][673][674].

7) Probable Mechanism: additive effects on the QT interval



**3.5.1.DW] 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[672][673][674]. 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[672][673][674].
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.DX] 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](#)[380] and the risk of QT-interval prolongation [381]. [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 [380]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [381].
- 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](#)[380] and the risk of QT-interval prolongation [381]. 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 [380]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [381].
- 7) Probable Mechanism: unknown; additive QT-interval prolongation

**3.5.1.DY] 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[495].
- 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.DZ] [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[600][601]. 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 [602].
- 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 agents, such as an angiotensin-converting enzyme inhibitor might be considered.
- 7) Probable Mechanism: decreased uptake of [guanadrel](#) into adrenergic neurons

### 3.5.1.EA] [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[440][441].
- 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 agents, such as an angiotensin-converting enzyme inhibitor, might be considered.
- 7) Probable Mechanism: decreased uptake of [guanethidine](#) into adrenergic neurons
- 8) Literature Reports

a) Doses of [doxepin](#) of 200 mg daily or more progressively produce blockade of the effects of [guanethidine](#) [434][435]. Antagonism of the effects of [guanethidine](#) developed slowly in one patient (over two to four days), even when given in a dose of 300 mg daily [doxepin](#). Two other patients experienced reversal of the hypotensive effects of [guanethidine](#) at doses of [doxepin](#) 200 to 300 mg daily. In all cases, the antagonism of antihypertensive effects was less than that of [desipramine](#) [434].

b) No antagonism of [guanethidine](#) was reported in two patients receiving [doxepin](#) 200 mg [436]. However, antagonism was observed at 300 mg doses [437]. A single case report describes a [hypertensive crisis](#) in a patient receiving [guanethidine](#) and [chlorpromazine](#) upon initiation of [doxepin](#) therapy less than 200 mg [438]. Doses of 300 mg a day or more will usually completely reverse the hypotensive effects of [guanethidine](#) [439].

### 3.5.1.EB] [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[133][134].

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.EC] [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[144][145][146][147][148]. Although no formal drug interaction studies have been done, coadministration of a tricyclic antidepressant with an antipsychotic is not recommended [149].

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](#) [143].

### 3.5.1.ED] [Halothane](#)

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

2) Summary: [Halothane](#) may prolong the QT interval in some patients[443]. 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 [444].

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 [halothane](#) and tricyclic antidepressants is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.EE] [Heptabarbital](#)

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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.EF] 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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.EG] 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[672][673][674]. 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[672][673][674].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EH] Hydroxychloroquine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: [Hydroxychloroquine](#) has been associated with QT interval prolongation[548][549], [ventricular premature contractions](#), and [torsade de pointes](#) [549]. 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[548][549]. 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 [548].

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 [549].

### 3.5.1.EI] Hydroxytryptophan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [doxepin](#) and hydroxytryptophan 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](#). Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [doxepin](#) and hydroxytryptophan are used concurrently.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [doxepin](#) 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.EJ] 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[668]. 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[668]. 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.EK] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.EL] [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[246], [amiodarone](#) [247], azimilide [248], [bretylium](#) [249], [ibutilide](#) [250], sematilide [251], [dofetilide](#) [252], and [sotalol](#) [253]. 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 [254][255].

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 [244].

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 [245].

### 3.5.1.EM] [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.EN] [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[442].

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[442].

7) Probable Mechanism: inhibition of [norepinephrine](#) transporter function by antidepressants

### 3.5.1.EO] [Iproniazid](#)

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in [serotonin syndrome](#)[737][738][739][740]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), [myoclonus](#), and changes in mental status [741]. If TCAs and MAOIs must be used concurrently, avoid large doses; use only oral TCAs; avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranlycypromine](#); and monitor patients closely [742][743].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and an MAOI should be done only with close monitoring and when the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. Consider using a 14-day washout period between

treatment with both medicines. If deemed clinically necessary, avoid large doses and use agents other than [imipramine](#), [clomipramine](#), [desipramine](#), or [tranylcypromine](#).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of MAOIs with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [726][727][728][729]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [730].

b) Administration of a tricyclic antidepressant (TCA) after MAOI therapy may result in the development of [serotonin syndrome](#). In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), 2 subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately 4 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 [731].

c) A drug interaction occurred in a 76-year-old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever that then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. Symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and resolved a few days after discontinuing all antidepressant medications [732].

d) 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 hyperpyrexia state led to DIC and eventual death [733].

e) There is evidence that MAOIs and tricyclic antidepressants (TCAs) can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in 1 of 2 ways. Most frequently, the recommendation is to stop all previous antidepressants (5 to 10 days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [734]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added [274]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [735][728][736].

### 3.5.1.EP] [Isocarboxazid](#)

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

2) Summary: The concurrent administration of [isocarboxazid](#) and [doxepin](#) is contraindicated[201]. 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](#) [202][203] [204][205]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation

characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [206]. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranlycypromine](#), and monitor patients closely [207][208].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: The concurrent use of [doxepin](#) and [isocarboxazid](#) is contraindicated. In patients being transferred to [isocarboxazid](#) therapy from a dibenzazepine-related entity, allow at least a one-week medication-free interval and then initiate [isocarboxazid](#) at one-half of the normal dose for at least the first week of therapy. Also allow one week to elapse between the discontinuation of [isocarboxazid](#) and the administration of another MAO inhibitor or dibenzazepine-related entity.

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 [183][184][185][186][187][188]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [189].

b) The development of [serotonin syndrome](#) was first 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 [190].

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 [191].

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 [192].

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 [193].

**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 [194].

**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 [195][185][186][196][197]. 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 [198]. 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 [198]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [199][186][200].

### 3.5.1.EQ| 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[753]. 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 [754].

**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.ER| 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[744][745].

**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.ES] 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[553].
- 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[553].
- 7) Probable Mechanism: additive QT-interval prolongation

**3.5.1.ET] Ketoconazole**

- 1) Interaction Effect: increased risk for QT prolongation
- 2) Summary: **Ketoconazole** has been shown to prolong the QT interval[348]. Caution is advised when using **ketoconazole** together with another agent known to cause QT interval prolongation. Concomitant use of **ketoconazole** with this drug may result in additive effects on the QT interval, increasing the risk for serious **ventricular arrhythmias**, including **torsades de pointes**.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: **Ketoconazole** has been shown to prolong the QT interval[348]. Caution is advised when using **ketoconazole** together with another agent known to cause QT interval prolongation. Concomitant use of **ketoconazole** with this drug may result in additive effects on the QT interval, increasing the risk for serious **ventricular arrhythmias**, including **torsades de pointes**.
- 7) Probable Mechanism: additive QT-interval prolongation

**3.5.1.EU] 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[533]. 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**[533]. 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 [533].

### 3.5.1.EV] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.EW] [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[672][673][674]. 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[672][673][674].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EX] [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[691]. If concomitant administration is required, monitor the patient closely.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) 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[691]. If concomitant administration is required, monitor the patient closely.
- 7) Probable Mechanism: potentiation of vascular effects

### 3.5.1.EY] [Levofloxacin](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: The concomitant use of [levofloxacin](#) together with another agent known to cause QT-interval prolongation should be avoided. Concomitant use may result in additive effects on the QT interval and increase the risk of cardiac adverse events, including [arrhythmia](#) and [torsade de pointes](#). The elderly and patients with risk factors for [torsade de pointes](#) (known QT prolongation, uncorrected hypokalemia) may be more susceptible to QT interval effects[751].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [levofloxacin](#) together with another agent known to cause QT-interval prolongation should be avoided. Concomitant use may result in additive effects on the QT interval and increase the risk of cardiac adverse events, including [arrhythmia](#) and [torsade de pointes](#). The elderly and patients with risk factors for [torsade de pointes](#) (known QT prolongation, uncorrected hypokalemia) may be more susceptible to QT interval effects[751].
- 7) Probable Mechanism: additive effects on QT interval

### 3.5.1.EZ] [Levomethadyl](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Levomethadyl can prolong the QT interval in some patients, which may result in [ventricular tachycardia](#), [ventricular fibrillation](#), and [torsades de pointes](#). Because [doxepin](#) may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of levomethadyl with [doxepin](#) is contraindicated[141][142].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of levomethadyl and [doxepin](#) is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.FA] [Levomilnacipran](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Levomilnacipran is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of potentially life-threatening [serotonin syndrome](#) and should be approached with extreme caution. If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the

coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[752].

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[752].

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.FB] [Levonorgestrel](#)

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].

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

8) Literature Reports

a) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

d) The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

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 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 [354].

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 [355].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.FC] [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[530]. 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[530]. 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.FD] [Linezolid](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hyperthermia](#), hyperreflexia, myoclonus, mental status changes)
- 2) Summary: Concomitant use of [linezolid](#) and a tricyclic antidepressant, such as [doxepin](#), is contraindicated in the absence of monitoring for [serotonin syndrome](#). If symptoms occur, consider discontinuation of either one or both of the drugs. [Linezolid](#) is a reversible, nonselective inhibitor of monoamine oxidase and may therefore interact with tricyclic antidepressants. Spontaneous reports of [serotonin syndrome](#) associated with the co-administration of [linezolid](#) and serotonergic agents have been reported[597].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [linezolid](#) and tricyclic antidepressants, such as [doxepin](#), is contraindicated unless patient is closely observed for signs and/or symptoms of [serotonin syndrome](#). If concomitant use is clinically warranted, monitor for signs and symptoms of [serotonin syndrome](#), such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary[99][597].
- 7) Probable Mechanism: [linezolid](#) inhibition of monoamine oxidase resulting in an increased concentration of serotonin

### 3.5.1.FE] [Lisdexamfetamine](#)

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[663].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[663].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

### 3.5.1.FF] Lorcaserin

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic neurotransmitter system, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life threatening and symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[162].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution with concomitant administration of lorcaserin and another serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops[162].
- 7) Probable Mechanism: additive serotonergic effects

### 3.5.1.FG] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.FH] [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[595] and use with caution [596].

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[595] and use with caution [596].

7) Probable Mechanism: additive CNS depression

### 3.5.1.FI] [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[533]. 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](#)[533]. 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 [533].

#### 3.5.1.FJ] 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[533]. 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](#)[533]. 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 [533].

#### 3.5.1.FK] 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[533]. 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](#)[533]. 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 [533].

**3.5.1.FL] Medroxyprogesterone Acetate**

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic antidepressant toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].
- 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
- 8) Literature Reports

a) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

**d)** The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

**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 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 [354].

**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 [355].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.FM] [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[533]. 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](#)[533]. 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 [533].

**3.5.1.FN] 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[533]. 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](#)[533]. 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 [533].

**3.5.1.FO] Meperidine**

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

**2)** Summary: [Meperidine](#) is considered a proserotonergic opioid and has been associated with [serotonin syndrome](#) when used concomitantly with other serotonergic agents[170]. Increased serotonin levels which may produce additive serotonergic effects can occur if serotonergic agents are taken concurrently with [meperidine](#). Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [99]. Use caution if [meperidine](#) and a serotonergic agent are coadministered and monitor patients for signs and symptoms of [serotonin syndrome](#).

**3)** Severity: major

**4)** Onset: unspecified

**5)** Substantiation: theoretical

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

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.FP] [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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.FQ] [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](#)[611].

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](#)[611].

7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.FR] [Mestranol](#)



- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic antidepressant toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].
- 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
- 8) Literature Reports

a) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

d)) The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

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 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 [354].

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 [355].

g)) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.FS] [Methamphetamine](#)

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

2)) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[663].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

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

and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[663].

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

### 3.5.1.FT] [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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.FU] [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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512] 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 [515][516][517][518].

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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

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

8J) Literature Reports

aJ) 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 [513].

bJ) 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 [514].

### 3.5.1.FV] Methylene Blue

1J) Interaction Effect: an increased risk of [serotonin syndrome](#) (labile blood pressure, [hyperthermia](#), neuromuscular abnormalities, mental status changes, gastrointestinal symptoms)

2J) Summary: Concurrent use of [doxepin](#) and methylene blue (an MAOI) is contraindicated[22] as this may result in potentially fatal [serotonin syndrome](#) [159]. There have been reports of serious reactions, including fatalities, in patients receiving concomitant tricyclic antidepressants and MAOIs [22]. If no alternative treatment is available and urgent methylene blue therapy is required for a patient on [doxepin](#) therapy, and the potential benefits outweigh the risk of [serotonin syndrome](#), [doxepin](#) must be discontinued immediately [160]. Use the lowest possible dose of methylene blue [159]. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. [Doxepin](#) may be resumed 24 hours after the last dose of methylene blue has been given [160].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Concurrent use of [doxepin](#) and methylene blue (an MAOI) is contraindicated[22]. Concurrent administration may result in potentially fatal [serotonin syndrome](#) [159]. In settings where urgent treatment with methylene blue is not required, discontinue [doxepin](#) at least 14 days prior to initiating treatment with methylene blue. If no alternative treatment is available and urgent methylene blue therapy is required for a patient on [doxepin](#) therapy, and the potential benefits outweigh the risk of [serotonin syndrome](#), [doxepin](#) must be discontinued immediately [160]. Use the lowest possible dose of methylene blue [159]. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. [Doxepin](#) may be resumed 24 hours after the last dose of methylene blue has been given [160].

7J) Probable Mechanism: inhibition of MAO-mediated serotonin metabolism by methylene blue

### 3.5.1.FW] 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[95]. 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 [96].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of tricyclic antidepressant with [metoclopramide](#) is contraindicated[95]. 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 [96].

7J) Probable Mechanism: unknown

### 3.5.1.FXJ [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[154].

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[154].

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 [154].

bJ) 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 [155].

### 3.5.1.FYJ [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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512] 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 [515][516][517][518].
- 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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512]. 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 [513].

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 [514].

### 3.5.1.FZ| [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[519]. 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 [99].
- 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](#)[519].



7J) Probable Mechanism: additive serotonin effects

8J) Literature Reports

aJ) Within a few hours of starting [mirtazapine](#) and shortly after stopping [fluoxetine](#), a 75-year-old woman experienced symptoms consistent with [serotonin syndrome](#). Current medication for depression included [fluoxetine](#), [chlorpromazine](#), and [lorazepam](#). Due to lack of response, [fluoxetine](#) was discontinued and soon afterward [mirtazapine](#) 30 mg/day was started. Within a few hours of starting [mirtazapine](#), she experience dizziness, headache, nausea, dry mouth, intense anxiety and agitation with suicidal ideas. Other symptoms were difficulty walking, marked resting tremor of the hands, and insomnia. Over the next 3 days, she progressively worsened. [Mirtazapine](#) was discontinued on day 5. Her symptoms improved the following day. [Fluoxetine](#) 20 mg/day was restarted on day 7 with subsequent resolution of dizziness, nausea, headache, and agitation resolution over the following days. Over the next 10 days, tremor, anxiety, difficulty walking, dry mouth, and insomnia improved [520].

bJ) A 26-year-old woman with [anorexia nervosa](#) receiving [fluvoxamine](#) for 4 months developed symptoms of [serotonin syndrome](#) after [mirtazapine](#) was initiated. The symptoms of twitching, tremors, agitation, restlessness, and "feeling like she could crawl out of her skin" developed over a period of 4 days after starting [mirtazapine](#) 30 mg/day. Symptoms rapidly progressed to twitching, tremors, and restlessness. She was hospitalized with further symptoms of diaphoresis, flushing, fasciculations, and nausea and treated with [ciproheptadine](#), [acetaminophen](#), and IV fluids. She remained afebrile throughout the event. Symptoms completely resolved within 24 hours [521].

### 3.5.1.GA] Moclobemide

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](#)[122][123][124][125]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [126]. Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranlycypromine](#), and monitor patients closely [127][128].

3J) Severity: contraindicated

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of moclobemide and a tricyclic antidepressant, such as [doxepin](#), is contraindicated. If [doxepin](#) is replacing treatment with moclobemide, a minimum of two days should elapse after moclobemide is discontinued and [doxepin](#) therapy is begun[101]. However, the manufacturer of [doxepin](#) recommends that the monoamine oxidase inhibitor (MAOI) be discontinued for at least 14 days before treatment with [doxepin](#) is initiated [102]. There is no specific washout period for replacing [doxepin](#) treatment with moclobemide. However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with and MAOI [103].

7J) Probable Mechanism: altered catecholamine uptake and metabolism

8J) Literature Reports

aJ) 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 [101]. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [104][105][106][107][108][109]. The

mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [110].

**b))** A clinical study designed to detect an interaction between moclobemide and a tricyclic antidepressant ([clomipramine](#)) resulted in severe adverse effects, and the study was terminated. Information about interactions with moclobemide and other tricyclic antidepressants is limited [101].

**c))** A drug interaction occurred in which a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching 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 [111].

**d))** Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). 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 [112].

**e))** 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 [113].

**f))** 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 [114].

**g))** 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 hyperpyrexial state led to [disseminated intravascular coagulation](#) and eventual death [115].

**h))** 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 [116][106][107][117][118]. 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 [119]. 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 [119]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [120][107][121].

### 3.5.1.GB| [Moricizine](#)

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

2) Summary: Concomitant use of tricyclic antidepressants, including [doxepin](#), and class IA antiarrhythmics, including [moricizine](#), may increase the risk of [cardiotoxicity](#) due to similar cardiac effects of these drugs[209][210]. Therefore, monitoring the patient for signs and symptoms of [cardiac toxicity](#) during coadministration of [doxepin](#) and [moricizine](#) may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [doxepin](#) and [moricizine](#) may increase the risk of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs[209][210]. 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) 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](#) [211].

### 3.5.1.GC| [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.GD] [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](#)[534] 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](#)[534] and monitor for changes in the QT-interval.

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

### 3.5.1.GE] [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.GF] Nafarelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[672][673][674]. 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[672][673][674].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GG] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.GH] Naratriptan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of a triptan and a tricyclic antidepressant may result in life-threatening [serotonin syndrome](#)[496]. Since triptans may be intermittently prescribed, potentially by a different physician, discuss the risks of [serotonin syndrome](#) and advise the patient to report signs or symptoms of [serotonin syndrome](#) (eg, [hypertension](#), [tachycardia](#), restlessness, [hyperthermia](#), hyperreflexia, incoordination).

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of a triptan and a tricyclic antidepressant may result in life-threatening [serotonin syndrome](#)[496]. Since triptans may be intermittently prescribed, potentially by a different physician, discuss the risks of [serotonin syndrome](#) and advise the patient to report signs or symptoms of [serotonin syndrome](#) (eg, [hypertension](#), [tachycardia](#), restlessness, [hyperthermia](#), hyperreflexia, incoordination).
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

### 3.5.1.GI] Nebivolol

- 1) Interaction Effect: increased exposure to nebivolol
- 2) Summary: Nebivolol is partially metabolized by the CYP2D6 isozyme. Concomitant use of nebivolol and a CYP2D6 inhibitor should be avoided[371] as it may increase plasma concentrations of nebivolol [371][372]. If coadministration is required, patients should be closely monitored, and dose adjustment may be required [372].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of nebivolol and a CYP2D6 inhibitor should be avoided[371] as it may increase plasma concentrations of nebivolol[371][372]. If coadministration is required, patients should be closely monitored, and dose adjustment may be required [372].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of nebivolol
- 8) Literature Reports

a) Coadministration of single dose of nebivolol 5 mg to healthy volunteers (n=23) who received [paroxetine](#) 20 to 40 mg/day for 6 days resulted in a 6.1-fold increase in nebivolol exposure and a 5.7-fold increase in the exposure of the nebivolol active metabolite. Significant increases were seen in nebivolol C<sub>max</sub> (1.78 to 4.24 ng/mL), T<sub>max</sub> (1.37 to 3.11 hours), and AUC (17.26 to 106.2 ng x hr/mL) [373].

b) Coadministration of a single 10-mg dose of nebivolol in healthy adults (n=10) who received [fluoxetine](#) at a dose of 20 mg/day for 21 days led to an 8-fold increase in AUC and 3-fold increase in C<sub>max</sub> of d-nebivolol (pharmacologically active isomer) [371].

### 3.5.1.GJ] Nefopam

- 1) Interaction Effect: an increased risk of seizures
- 2) 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[94].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) 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.
- 7) Probable Mechanism: additive lowering of seizure threshold



**3.5.1.GK] Nepafenac**

- 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[533]. 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](#)[533]. 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 [533].

**3.5.1.GL] 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[533]. 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](#)[533]. 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 [533].

**3.5.1.GM] 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[533]. 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](#)[533]. 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 [533].

#### 3.5.1.GN] 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[533]. 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](#)[533]. 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 [533].

#### 3.5.1.GO] Norelgestromin

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].

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

8) Literature Reports

a) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

d)) The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

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 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 [354].

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 [355].

g)) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.GP] [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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512] 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 [515][516][517][518].

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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

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

8J) Literature Reports

aJ) 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 [513].

bJ) 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 [514].

### 3.5.1.GQJ [Norethindrone](#)

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

2J) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].

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

8J) Literature Reports

aJ) Some studies 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 [349].

**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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

**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 [352].

**d)** The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

**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 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 [354].

**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 [355].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.GR] Norgestimate

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].

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

8) Literature Reports

a) Some studies 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 [349].

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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

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 [352].

**d))** The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

**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 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 [354].

**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 [355].

**g))** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.GS] [Norgestrel](#)

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

**2))** Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[358], with paradoxical loss of antidepressant effect yet tricyclic antidepressant toxicity being manifested simultaneously [359]. The effects of the interaction appear to be estrogen dose-related [360] and may be of clinical importance primarily in patients previously stabilized on tricyclic antidepressant therapy who are being started on [estrogen therapy](#) [361].

**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

**8j) Literature Reports**

**aj)** Some studies 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 [349].

**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 [350]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants effects secondary to estrogen inhibition of hepatic microsomal enzymes [351].

**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 [352].

**dj)** The effect of oral contraceptives on [clomipramine](#) was studied 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 [353].

**ej)** The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. 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 [354].

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 [355].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [356]. 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 [357].

### 3.5.1.GT] [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[345][346]. 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 [347].
- 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.GU] [Ondansetron](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Ondansetron](#) prolongs the QT interval in a dose-dependent manner and postmarketing cases of [torsade de pointes](#) have been reported. Concomitant use of [ondansetron](#) with other QT-prolonging drugs may result in additive prolongation of the QT interval. If coadministration is necessary, [ECG monitoring](#) is recommended[634][635].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Ondansetron](#) prolongs the QT interval in a dose-dependent manner. Use caution with concomitant use of [ondansetron](#) and drugs known to prolong the QT interval. If coadministration is necessary, [ECG monitoring](#) is recommended[634][635].

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

### 3.5.1.GV] Oxaprozin

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[533]. 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](#)[533]. 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 [533].

### 3.5.1.GW] Oxilofrine

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

2J) 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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512] 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 [515][516][517][518].

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: probable

6J) 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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512]. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

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

8J) Literature Reports

aJ) 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 [513].

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 [514].

### 3.5.1.GX] [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[507].
- 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[507].
- 7)) Probable Mechanism: additive serotonergic effect

### 3.5.1.GY] [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[129].
- 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[129].
- 7)) Probable Mechanism: increased sympathomimetic activity

### 3.5.1.GZ] [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[649]. 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[649]. Dose reductions of one or both agents may be warranted.

7) Probable Mechanism: unknown; additive respiratory and CNS depressant effects

### 3.5.1.HA] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.HB] 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](#)[623].

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](#)[623].

7) Probable Mechanism: unknown

### 3.5.1.HC] 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[470].

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[470].

7) Probable Mechanism: additive QT effects

### 3.5.1.HD] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.HE] Pargyline

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in [serotonin syndrome](#)[706][707][708][709]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [710]. If TCAs and MAOIs must be used concurrently, avoid large doses; use only oral TCAs; avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranlycypromine](#); and monitor patients closely [711][712].

3) Severity: major

4) Onset: delayed

**5) Substantiation: probable**

**6) Clinical Management:** Concomitant use of a tricyclic antidepressant (TCA) and an MAOI should be done only with close monitoring and when the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If use is deemed clinically necessary, avoid large doses and use agents other than [imipramine](#), [clomipramine](#), [desipramine](#), or [tranylcypromine](#).

**7) Probable Mechanism:** altered catecholamine uptake and metabolism

**8) Literature Reports**

**a)** Concomitant administration of MAOIs with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [695][696][697][698]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [699].

**b)** Administration of a tricyclic antidepressant (TCA) after MAOI therapy may result in the development of [serotonin syndrome](#). In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), 2 subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately 4 weeks and subsequent [clomipramine](#) therapy. After taking the first 100-mg dose of [clomipramine](#), 1 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. Symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [700].

**c)** A drug interaction occurred in a 76-year-old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever that 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 [701].

**d)** 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 hyperpyrexia state led to DIC and eventual death [702].

**e)** There is evidence that MAOIs and tricyclic antidepressants (TCAs) can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in 1 of 2 ways. Most frequently, the recommendation is to stop all previous antidepressants (5 to 10 days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [703]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added [274]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [704][697][705].

**3.5.1.HF] [Paroxetine](#)**

**1) Interaction Effect:** increased risk of QT interval prolongation; increased risk of [serotonin syndrome](#); increased CYP2D6 substrate exposure

**2) Summary:** Coadminister [paroxetine](#) (a CYP2D6 inhibitor) cautiously with drugs that are QT-prolonging, serotonergic CYP2D6 substrates. Monitor for [serotonin syndrome](#) with concurrent use,

especially during treatment initiation or dose increases, and immediately discontinue and immediately discontinue [paroxetine](#) and other serotonergic agents if symptoms occur. Dose reduction of either [paroxetine](#) or a CYP2D6 substrate may be required, as Cmax and AUC of a single dose of [desipramine](#) (a CYP2D6 substrate), rose by 2- and 5-fold, respectively, when added to an existing regimen with [paroxetine](#). [Paroxetine](#) is also associated with [ventricular tachycardia](#) and [torsade de pointes](#)[163]; monitor for signs of additive prolongation of the QT interval during concurrent use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadminister cautiously with drugs that are QT-prolonging, serotonergic CYP2D6 substrates. Monitor for [serotonin syndrome](#) with concurrent use, especially during treatment initiation or dose increases, and immediately discontinue [paroxetine](#) and other serotonergic agents if symptoms occur. Dose reduction of either [paroxetine](#) (a CYP2D6 inhibitor) or a CYP2D6 substrate may be required. [Paroxetine](#) is also associated with [ventricular tachycardia](#) and [torsade de pointes](#)[163]; monitor for signs of additive prolongation of the QT interval during concurrent use.

7) Probable Mechanism: additive QT-prolonging effects; additive serotonergic effects; inhibition of CYP2D6 substrate metabolism by [paroxetine](#)

8) Literature Reports

a) 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 [163].

### 3.5.1.HG) Pasireotide

1) Interaction Effect: increased risk of QT prolongation

2) Summary: Pasireotide is associated with QT-interval prolongation. In 2 studies, QT prolongation occurred at both therapeutic and supratherapeutic doses of pasireotide. Concomitant administration of pasireotide with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval. ECGs at baseline and at 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents[557].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of pasireotide and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation of the QT interval. ECGs at baseline and 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents[557].

7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.HH) Pazopanib

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

2) Summary: Due to the potential for additive effects on QT-interval prolongation and increased risk of [torsade de pointes](#), coadministration of pazopanib with drugs that prolong the QT interval should be done cautiously. Baseline and periodic [monitoring of ECG](#) and electrolyte maintenance (eg, [calcium](#), [magnesium](#), [potassium](#)) within the normal range is recommended[570].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6J) Clinical Management: Coadministration of pazopanib with this drugs that prolong the QT interval should be done cautiously due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#). Baseline and periodic [monitoring of ECG](#) and electrolyte maintenance (eg, [calcium](#), magnesium, potassium) within the normal range is recommended[570].

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

### 3.5.1.HJ] Peginterferon Alfa-2b

1J) 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

2J) 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[620]. 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 [621]. 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 [620].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) 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[620].

7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of tricyclic antidepressants by peginterferon alfa-2b

8J) Literature Reports

aJ) 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 [621].

### 3.5.1.HJ] [Pentamidine](#)

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

2J) Summary: Tricyclic antidepressants (TCAs) and [pentamidine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[560][561]. 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 [562].

3J) Severity: major

4J) Onset: unspecified

5J) 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.HK] [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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.HL] [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](#)[305][306][307][308]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), [myoclonus](#), and changes in mental status [309]. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#), and monitor patients closely [310][311].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as [doxepin](#), and a monoamine oxidase inhibitor (MAOI), such as [phenelzine](#), should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#). If [doxepin](#) is replacing treatment with [phenelzine](#), a



minimum of 14 days should elapse after [phenelzine](#) is discontinued before [doxepin](#) therapy begins[257]. The manufacturer of [phenelzine](#) recommends a minimum of 10 days should elapse between discontinuing the tricyclic antidepressant therapy and initiating treatment with [phenelzine](#) [286].

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 [287][288][289][290][291][292]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [293].

b) Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). 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 [294].

c) A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching 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 [295].

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 [296].

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 [297].

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 [298].

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 [299][289][290][300][301]. 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 [302]. 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 [302]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [303][290][304].

### 3.5.1.HM] Phenindione

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[394][395]. Considerable interindividual differences may be found [396].
- 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 [391]. 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 [392]. 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 [393]. 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.HN] 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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.HO) Phenprocoumon

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[377][378]. Considerable interindividual differences may be found [379].

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 [374]. 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 [375]. 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 [376]. 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.HP] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.HQ] 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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512] 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 [515][516][517][518].
- 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[511]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [512]. 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 [513].

**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 [514].

### 3.5.1.HR] [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](#). 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[181][182].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor therapeutic efficacy of [doxepin](#); 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.HS] [Piketopifen](#)

- 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.HT] [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](#)[97].
- 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](#)[97].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.HU] 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](#)[175].
- 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](#)[175].
- 7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.HV] Piperaquine

- 1) Interaction Effect: increased exposure of CYP2C19 substrates and increased risk of QT interval prolongation
- 2) Summary: Concomitant administration of piperaquine and QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperaquine administration, is contraindicated. Concurrent administration of piperaquine (a CYP2C19 inhibitor) and a CYP2C19 substrate may increase the exposure of the CYP2C19 substrate. Due to the long half-life of piperaquine, caution is advised[509] when administering a CYP2C19 substrate for up to 3 months after discontinuation of piperaquine therapy .
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of piperaquine (a QT-interval prolonging drug) with other QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperaquine administration, is contraindicated. Concurrent administration of piperaquine (a CYP2C19 inhibitor) and a CYP2C19 substrate may increase the exposure of the CYP2C19 substrate. Due to the long half-life of piperaquine, caution is advised[509] when administering a CYP2C19 substrate for up to 3 months after discontinuation of piperaquine therapy .
- 7) Probable Mechanism: inhibition of CYP2C19-mediated metabolism of this drug by piperaquine; additive QT interval prolongation



**3.5.1.HW] 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[533]. 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](#)[533]. 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 [533].

**3.5.1.HX] 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[599].
- 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[599].
- 7) Probable Mechanism: additive QT prolongation

**3.5.1.HY] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.HZJ [Primidone](#)

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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.IAJ [Procainamide](#)

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

2J) Summary: Concomitant use of tricyclic antidepressants, including [doxepin](#), and class IA antiarrhythmics, including [procainamide](#), may increase the risk of [cardiotoxicity](#) due to similar cardiac effects of these drugs[209][210]. Therefore, monitoring the patient for signs and symptoms of [cardiac toxicity](#) during coadministration of [doxepin](#) and [procainamide](#) may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6) Clinical Management: Concomitant use of [doxepin](#) and [procainamide](#) may increase the risk of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs[209][210]. 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) 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](#) [211].

### 3.5.1.IB) 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[588][589]. Concurrent use is not recommended [590].

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use is not recommended and should probably be initiated only under close medical supervision, and then only if other antidepressant class agents have proven unsuccessful. With more potent MAOIs, recommendations for concurrent use of TCAs have included avoiding large doses of the TCA, using only oral tricyclics, and avoiding [imipramine](#), [clomipramine](#), and [desipramine](#). [Procarbazine](#) therapy should not begin until seven days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors.

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 [577]. Animal studies have indicated that [procarbazine](#) is a monoamine oxidase inhibitor (MAOI) [578] but appears to be a relatively weak MAOI in man [577]. Hypertensive reactions may still result from concomitant administration of tricyclic antidepressants, sympathomimetics, and tyramine containing foods [577][579].

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 [580][581][582][583][584][585]. 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 [586].

c) **Procarbazine** therapy should not begin until 7 days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors [587][577].

### 3.5.1.IC] **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[312][313][314]. Other phenothiazines may have similar effects, though no reports are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation [315]. 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 [316][317][318][319].

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.ID] **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[533]. 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**[533]. 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 [533].

### 3.5.1.IE] **Propafenone**

1) Interaction Effect: **doxepin** toxicity (sedation, dry mouth)

2) Summary: A single case was reported in which coadministration of **propafenone** and **desipramine** in an elderly patient resulted in **desipramine** toxicity at a **desipramine** dosage which had previously produced levels in the therapeutic range[546]. Although not reported for **doxepin**, caution should be used with concomitant use of **propafenone**.

- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for symptoms of tricyclic antidepressant toxicity.
- 7) Probable Mechanism: decreased [doxepin](#) metabolism
- 8) Literature Reports

a) A 68-year-old man suffering from agitated [major depression](#) was started 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 [545].

### 3.5.1.IF] [Propoxyphene](#)

- 1) Interaction Effect: [doxepin](#) toxicity (sedation, lethargy, dry mouth, urinary retention)
- 2) Summary: Concomitant therapy with [propoxyphene](#) and [doxepin](#) has been reported to double steady state [doxepin](#) and desmethyldoxepin plasma concentrations and decrease cognitive function. This interaction is most likely related to inhibition of hepatic microsomal enzymes by [propoxyphene](#)[591].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for symptoms of tricyclic antidepressant toxicity such as sedation, dry mouth, and urinary retention. Serum [doxepin](#) levels may also be of value in predicting toxicity. An alternative analgesic agent such as [acetaminophen](#) with [codeine](#) might be considered if clinically appropriate.
- 7) Probable Mechanism: decreased [doxepin](#) metabolism

### 3.5.1.IG] [Propranolol](#)

- 1) Interaction Effect: postural hypotension
- 2) Summary: Coadministration of [propranolol](#) and a tricyclic antidepressant (TCA) may result in exacerbation of the hypotensive effect of the TCA. If concomitant use is required, monitor patients for postural hypotension[642].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [propranolol](#) and a tricyclic antidepressant (TCA) may result in exacerbation of the hypotensive effect of the TCA and should be undertaken with caution. If concomitant use is required, monitor patients for postural hypotension[642].
- 7) Probable Mechanism: exacerbation of tricyclic antidepressant-induced hypotension by [propranolol](#)

### 3.5.1.IH] [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.II] 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.IJ] 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[229].



- 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[229].
- 7) Probable Mechanism: additive effects on QT interval

### 3.5.1.IK] [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[240], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [241]. The effects of the interaction appear to be estrogen dose-related [242] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [243].
- 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) 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 [231].

b) A case reported by [232] 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 [233].

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 [234].

d) The effect 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 [235].

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 [236].

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 [237].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [238]. 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 [239].

### 3.5.1.IL] [Quinidine](#)

1) Interaction Effect: increased [doxepin](#) plasma concentrations; an increased risk of [cardiotoxicity](#)

2) Summary: Concomitant use of [doxepin](#), a CYP2D6 substrate, and [quinidine](#), a CYP2D6 inhibitor, may result in increased [doxepin](#) exposure[22]. The incidence of [cardiotoxicity](#) may also be increased if tricyclic antidepressants are administered with class IA antiarrhythmics due to similar cardiac effects of these drugs [209][210]. Monitoring the patient for increased [doxepin](#) side effects during concomitant use and for [doxepin](#) efficacy after [quinidine](#) discontinuation may be warranted. The patient may also need to be monitored for signs and symptoms of [cardiac toxicity](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of **doxepin** and **quinidine** may result in increased **doxepin** exposure[22]. 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 [209][210]. Monitor for increased **doxepin** side effects if **doxepin** is coadministered with **quinidine**. Conversely, if **quinidine** is discontinued from therapy, monitor for **doxepin** efficacy. Also monitor the patient for signs and symptoms of **cardiac toxicity**, including any changes in the ECG.

7) Probable Mechanism: inhibition of CYP2D6 **doxepin** metabolism by **quinidine**; additive **cardiac toxicity**

8) Literature Reports

a) 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** [211].

### 3.5.1.IM] **Ramelteon**

1) Interaction Effect: increased **ramelteon** exposure

2) Summary: Concomitant use of **doxepin** and **ramelteon** increased **ramelteon** exposure. When a single 8-mg dose of **ramelteon** was administered to patients who had already been receiving **doxepin** 10 mg once daily for 23 days, there were mean increases in **ramelteon** AUC and Cmax of approximately 66% and 69%, respectively, compared with **doxepin** therapy alone; there was no change in M-II exposure. Therefore, patients should be closely monitored when **doxepin** and **ramelteon** are coadministered[508].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of **doxepin** and **ramelteon** resulted in increased **ramelteon** Cmax and AUC. Therefore, closely monitor the patient when **doxepin** and **ramelteon** are coadministered[508].

7) Probable Mechanism: unknown

### 3.5.1.IN] **Ranolazine**

1) Interaction Effect: increased tricyclic antidepressant plasma concentrations

2) 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[510].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6J) 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[510].

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

### 3.5.1.IOJ [Rasagiline](#)

1J) Interaction Effect: severe CNS toxicity

2J) 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[140].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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[140].

7J) Probable Mechanism: unknown

### 3.5.1.IPJ [Risperidone](#)

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[144][145][146][147][148]. Although no formal drug interaction studies have been done, coadministration of a tricyclic antidepressant with an antipsychotic is not recommended [149].

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](#) [143].

### 3.5.1.IQJ [Ritonavir](#)

1J) Interaction Effect: increased [doxepin](#) serum concentrations

- 2) Summary: The concurrent administration of [doxepin](#), a tricyclic antidepressant metabolized by CYP2D6[218], and [ritonavir](#), a CYP2D6 inhibitor, may result in increased [doxepin](#) serum levels. If coadministration is necessary, monitoring of [doxepin](#) levels is recommended [218], and a decrease in [doxepin](#) dose may be necessary [472][473].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [doxepin](#) and [ritonavir](#) as this may lead to increased [doxepin](#) serum levels. Increased monitoring and/or a decrease in [doxepin](#) dose [doxepin](#) may be necessary[218][472][473].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [doxepin](#) metabolism

### 3.5.1.IR| [Rofecoxib](#)

- 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.IS| 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 (SAME) and [clomipramine](#)[387]. SAME was shown to hasten the onset of therapeutic response of [imipramine](#) in a clinical trial involving 40 patients, without serotonergic side effects [388]. If therapy is initiated with SAME 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 [389].
- 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 mm<sup>3</sup>, 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](#) [386].

### 3.5.1.IT] 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[397].

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[397].

7) Probable Mechanism: Additive serotonergic effects

### 3.5.1.IU] Salicylic 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[533]. 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](#)[533]. 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 [533].

#### 3.5.1.IV] Salmeterol

1) Interaction Effect: an increased risk of cardiovascular excitation

2) 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[130]. 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.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) 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.

7) Probable Mechanism: potentiation of vascular effects

#### 3.5.1.IW] Salsalate

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[533]. 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](#)[533]. 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 [533].

**3.5.1.IX] 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[499].

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[499].

7) Probable Mechanism: additive QT interval effects

**3.5.1.IY] 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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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] 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](#)[338][339][340][341]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), [myoclonus](#), and changes in mental status [342]. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranlycypromine](#), and monitor patients closely [343][344].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as [doxepin](#), and a monoamine oxidase inhibitor (MAOI), such as [selegiline](#), should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than [imipramine](#), [clomipramine](#), [desipramine](#), and [tranlycypromine](#). A minimum of 14 days should elapse after [selegiline](#) is discontinued before [doxepin](#) therapy begins[257]. There is no specific washout period for [doxepin](#) when beginning treatment with [selegiline](#). However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with the MAOI [103].
- 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 [320][321][322][323][324][325]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [326].

b) Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). 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 [327].

c) A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching 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 [328].

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 [329].

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 [330].

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 [331].

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 [332] [322][323][333][334]. 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 [335]. 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 [335]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [336][323][337].

### 3.5.1.JA] 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[246], [amiodarone](#) [247], azimilide [248], [bretylum](#) [249], [ibutilide](#) [250], sematilide [251], [dofetilide](#) [252], and [sotalol](#) [253]. 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 [254][255].

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 [244].

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 [245].

### 3.5.1.JB| 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[144][145][146][147][148]. Although no formal drug interaction studies have been done, coadministration of a tricyclic antidepressant with an antipsychotic is not recommended [149].

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](#) [143].

### 3.5.1.JC| 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[547].

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[547].

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

### 3.5.1.JD] [Sevoflurane](#)

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

2J) Summary: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#)[166].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#)[166].

7J) Probable Mechanism: additive effects on QT interval

### 3.5.1.JE] [Sodium 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.JF] [Sotalol](#)

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[246], [amiodarone](#) [247], azimilide [248], [bretylium](#) [249], [ibutilide](#) [250], sotalol [251], [dofetilide](#) [252], and [sotalol](#) [253]. 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 [254][255].



- 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 [244].

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 [245].

#### 3.5.1.JG| [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](#)[498].
- 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](#)[498].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.JH| [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[550][551]. 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 [552].
- 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.JI| [St John's Wort](#)

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

2) Summary: Theoretically, since St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity[222][223], [serotonin syndrome](#) could result when St. John's Wort is taken along with a tricyclic antidepressant. 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 [224], as well as concomitant use of monoamine oxidase inhibitors with tricyclic antidepressants [225][226][227]. Coadministration of [amitriptyline](#) and St. John's Wort decreased the area under the concentration-time curve of [amitriptyline](#) and its metabolite [nortriptyline](#) [228]; if other tricyclic antidepressants are similarly affected by St. John's Wort, the risk of [serotonin syndrome](#) may be reduced, yet effectiveness of the tricyclic antidepressant may also be reduced. To maintain maximal effectiveness of the tricyclic antidepressant, as well as avoid any potential risk of [serotonin syndrome](#), avoid concomitant use of St. John's Wort and tricyclic antidepressants.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of St. John's Wort with tricyclic antidepressants.

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

### 3.5.1.JJ| [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[382][383]. 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 [384].

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.JK| [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.JL] 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[131].
- 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[131].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.JM] 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[144][145][146][147][148]. Although no formal drug interaction studies have been done, coadministration of a tricyclic antidepressant with an antipsychotic is not recommended [149].
- 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](#) [143].

### 3.5.1.JN] 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[669][670][671].

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[669][670][671].

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

### 3.5.1.JO| Suvorexant

1) Interaction Effect: additive sedative effects

2) Summary: Avoid concomitant use of suvorexant and this drug as potentiation of sedative effects may occur[558].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of suvorexant and this drug is not recommended as potentiation of sedative effects may occur[558].

7) Probable Mechanism: additive CNS depression

### 3.5.1.JP| [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[593][594].

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[593][594].

7) Probable Mechanism: additive effects on QT interval

### 3.5.1.JQ| 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[178].

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[178].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.JR| 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[246], [amiodarone](#) [247], azimilide [248], [bretylum](#) [249], [ibutilide](#) [250], sotalol [251], [dofetilide](#) [252], and [sotalol](#) [253]. 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 [254][255].

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 [244].

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 [245].

### 3.5.1.JS| 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[220]. 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 [221].

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.JT| 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[533].

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](#)[533]. 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 [533].

### 3.5.1.JU] [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](#)[497].

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](#)[497].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.JV] [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[475][476][477]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [478]. 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 [474]. 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.JW] [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](#)[138].
- 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](#)[138].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.JX] [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.JY| 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[490], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [491]. The effects of the interaction appear to be estrogen dose-related [492] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [493].

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) Some studies 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 [481].

b) A case reported by [482] 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 [483].

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 [484].

d) The effect of oral contraceptives on [clomipramine](#) was studied 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 [485].

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 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 [486].

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 [487].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [488]. 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 [489].

### 3.5.1.JZ| [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[569].
- 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[569].
- 7) Probable Mechanism: additive anticholinergic effects

### 3.5.1.KA| 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.KB] [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[533]. 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](#)[533]. 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 [533].

### 3.5.1.KC] [Tramadol](#)

1) Interaction Effect: an increased risk of seizures, [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes), opioid toxicity, and increased concentrations of [tramadol](#) and decreased concentrations of [tramadol](#) active metabolite, M1

- 2) Summary: Caution is advised with concomitant use of [doxepin](#) and [tramadol](#). [Doxepin](#) is a tricyclic antidepressant (TCA) with serotonergic activity and is a CYP2D6 inhibitor. Concomitant use of [tramadol](#) with a tricyclic antidepressant (TCA) or an agent with serotonergic activity may increase the risk for seizures and [serotonin syndrome](#) even if [tramadol](#) is used within the recommended dosage range. Additionally, concomitant use of [tramadol](#) and CYP2D6 inhibitors can decrease metabolism of [tramadol](#) to the active metabolite, M1, potentially causing reduced analgesia. Furthermore, elevated [tramadol](#) concentrations because of inhibition of CYP2D6-mediated metabolism may cause opioid toxicity. If concomitant use of [tramadol](#) with a serotonergic agent or TCA is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation and dose increases[362]. Consider monitoring patients for signs and symptoms of narcotic toxicity or decreased analgesic effect of [tramadol](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised with concomitant use of [doxepin](#) and [tramadol](#). Concomitant use of [tramadol](#) with a tricyclic antidepressant (TCA) or an agent with serotonergic activity may increase the risk for seizures and [serotonin syndrome](#), even if [tramadol](#) is used within the recommended dosage range. Additionally, opioid toxicity and reduced analgesia may occur. If concomitant use of [tramadol](#) with a TCA or serotonergic agent is clinically warranted, careful observation is recommended, particularly during treatment initiation and dose increases[362]. Consider monitoring patients for signs and symptoms of opioid toxicity as well as decreased analgesic effect of [tramadol](#).
- 7) Probable Mechanism: lowered seizure threshold; additive serotonergic effects; inhibition of CYP2D6-mediated [tramadol](#) metabolism

### 3.5.1.KD| [Tranlycypromine](#)

- 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](#)[277][278][279][280]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [281]. Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranlycypromine](#), and monitor patients closely [282][283].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [doxepin](#) with a monoamine oxidase inhibitor (MAOI), such as [tranlycypromine](#) is contraindicated[256]. If [doxepin](#) is replacing treatment with [tranlycypromine](#), a minimum of 14 days should elapse after [tranlycypromine](#) is discontinued before therapy with [doxepin](#) begins [257]. The manufacturer of [tranlycypromine](#) recommends that at least 7 days should elapse before [tranlycypromine](#) therapy is replaced by [doxepin](#). Similarly, if [doxepin](#) therapy is substituted by [tranlycypromine](#), there should be a 7 day washout period. [Tranlycypromine](#) should then be given using half the normal starting dosage for, minimally, the first week of therapy [256].
- 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 [256]. Reports of excitation, [hyperpyrexia](#), convulsions,

and possible death have been attributed to the combination [258][259][260][261][262][263]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [264].

**b))** Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). 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 [265].

**c))** A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching 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 [266].

**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 [267].

**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 [268].

**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 [269].

**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 [270] [260][261][271][272]. 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 [273]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added [274]. Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [273]. Numerous



studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [275][261][276].

### 3.5.1.KE] Trazodone

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

2) Summary: Both [doxepin](#) and [trazodone](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive effects and the potential for increased risk of [serotonin syndrome](#)[592]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [doxepin](#) and [trazodone](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [99].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [doxepin](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[592]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.KF] 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[312][313][314]. Other phenothiazines may have similar effects, though no reports are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation [315]. 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 [316][317][318][319].

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.KG] 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[382][383]. 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 [384].

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.KH] 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[672][673][674]. 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[672][673][674].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.KI] Valdecixib

- 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[533]. 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](#)[533]. 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 [533].

### 3.5.1.KJ] Vandetanib

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Vandetanib is associated with QT-interval prolongation. [Torsades de pointes](#), [ventricular tachycardia](#), and sudden death have also been reported in patients taking vandetanib. Therefore, avoid concurrent use of other QT-interval-prolonging agents as this may increase the risk of additive QT-interval

prolongation and [torsade de pointes](#). If coadministration is required, monitor ECG more frequently than during vandetanib monotherapy[647].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of vandetanib with another drug known to prolong QT interval should be avoided due to increased risk of additive QT-interval prolongation and [ventricular arrhythmias](#). Monitor ECG frequently if coadministration is required[647].

7J) Probable Mechanism: additive effects on QT interval

### 3.5.1.KK] [Vasopressin](#)

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

2J) Summary: Tricyclic antidepressants and [vasopressin](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[535][536][537][538][539][540][541][542][543][544]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as tricyclic antidepressants and [vasopressin](#), is not recommended.

7J) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.KL] [Vemurafenib](#)

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

2J) 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](#)[132].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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](#)[132].

7J) Probable Mechanism: additive effects on QT interval

### 3.5.1.KM] [Venlafaxine](#)

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

2J) Summary: Tricyclic antidepressants (TCAs) and [venlafaxine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[502][503]. 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 [504]. In addition, [venlafaxine](#) and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [505][502][506]. [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 [501].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

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

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

8) Literature Reports

a) When administered with [imipramine](#), the pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected. [Venlafaxine](#) increased the area under the concentration-time curve (AUC), maximum concentration (C<sub>max</sub>), and minimum concentration (C<sub>min</sub>) 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 [501].

### 3.5.1.KN] Vilanterol

1) Interaction Effect: an increased risk of cardiovascular adverse effects

2) 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[479]. If coadministration is required, monitor patients closely for adverse cardiovascular effects.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) 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[479]. If coadministration is necessary, monitor patients closely for adverse cardiovascular effects.

7) Probable Mechanism: potentiation of adrenergic agonist effects on the cardiovascular system

### 3.5.1.KO] Vilazodone

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

2) Summary: [Serotonin syndrome](#) has been reported with vilazodone monotherapy and in combination with other serotonergic drugs; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#)[139]. 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 [99]. 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 [139].

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with vilazodone monotherapy and in combination with other serotonergic drugs; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use and monitor for [serotonin syndrome](#). Discontinue use of vilazodone and concomitant serotonergic agents immediately if symptoms of [serotonin syndrome](#) emerge[139].
- 7) Probable Mechanism: additive serotonergic effects

### 3.5.1.KP] Vinflunine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Vinflunine is associated with QT-interval prolongation. Concomitant administration of vinflunine with other drugs that prolong the QT interval may have additive prolonging effects on the QT interval and is not recommended[174]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring when vinflunine is coadministered with other QT-prolonging agents.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of vinflunine and QT-prolonging drugs may result in additive QT-interval prolongation effects and is therefore not recommended[174]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.KQ] Vortioxetine

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Vortioxetine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with caution. [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[675].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of vortioxetine with serotonergic agents may increase the risk for [serotonin syndrome](#) and should be undertaken with caution. If concomitant use of vortioxetine with a serotonergic agent is clinically warranted, close monitoring of the patient is recommended, particularly during treatment initiation and dosage increases. If [serotonin syndrome](#) develops, discontinue vortioxetine and concomitant serotonergic agents and initiate supportive care[675].
- 7) Probable Mechanism: additive serotonergic effects

### 3.5.1.KR] Warfarin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[574][575]. Considerable interindividual differences may be found [576].

- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: In patients receiving [doxepin](#) and [warfarin](#) concurrently, the prothrombin time ratio or [international normalized ratio](#) (INR) should be closely monitored for stability of the anticoagulant response. Adjustment of the [warfarin](#) dosage may be required 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 [571]. 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 [572]. 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 [573]. 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.KS| [Ziprasidone](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[522][523]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[522][523]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.KT| [Zolmitriptan](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) and [zolmitriptan](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[526][527]. 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 [528].



- 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.KU] 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[144][145][146][147][148]. Although no formal drug interaction studies have been done, coadministration of a tricyclic antidepressant with an antipsychotic is not recommended [149].
- 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](#) [143].

### 3.5.1.KV] 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[603][604].
- 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[603][604].
- 7J) Probable Mechanism: additive QT prolongation

## 3.5.2] Drug-Food Combinations

### 3.5.2.A] Ethanol

- 1)) Interaction Effect: enhanced drowsiness; 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[761][762][763][764][765]. There are no studies evaluating respiratory response with the combination.
- 3)) Severity: moderate
- 4)) Onset: rapid
- 5)) Substantiation: theoretical
- 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.
- 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 [756].

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](#) [757].

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 [758].

d)) Individual case reports have documented "blackouts" following modest amounts of alcohol in combination with either [amitriptyline](#) or [imipramine](#) [759], and reversible extrapyramidal effects (parkinsonian effects, [akathisia](#)) with [amoxapine](#) [760].

## 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)) [Doxepin](#) Hydrochloride

##### 1)) Therapeutic

##### a)) Physical Findings

##### 1)) Depression and/or Anxiety

a)) Improvement in signs and symptoms of anxiety and/or depression is indicative of efficacy.

**b)** Improvement in the signs and symptoms of anxiety is often apparent before improvement in the signs and symptoms of depression. Optimal antidepressant effect may not be evident for 2 to 3 weeks [42].

**2)** Insomnia

**a)** Improvement in sleep maintenance is indicative of efficacy.

**3)** Pruritus associated with eczematous dermatitis, atopic dermatitis, or lichen simplex chronicus

**a)** Improvement in itching is indicative of efficacy.

**2)** Toxic

**a)** Physical Findings

**1)** Monitor for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial few months of therapy or at times of dose changes, either increases or decreases. Such monitoring should include daily observation by families and caregivers [22] [42].

**2)** Reevaluate insomnia if symptoms persists after 7 to 10 days of treatment [22].

#### **4.2] Patient Instructions**

**A)** [Doxepin](#) (By mouth)

[Doxepin](#)

Treats depression, anxiety, and sleep disorders. This medicine is a 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 [doxepin](#) or similar medicines.

How to Use This Medicine:

Capsule, Liquid, Tablet

Your doctor will tell you how much medicine to use. Do not use more than directed.

[Sinequan](#)® oral liquid:

Measure the dose with the dropper that comes with the medicine.

Mix the medicine with 120 mL (4 ounces) of water, milk, or fruit juice (orange, grapefruit, tomato, prune, or pineapple) before you drink it. Do not use grape juice or carbonated beverages (soda pop).

Mix the medicine just before you take your dose. Do not prepare it ahead of time.

[Silenor](#)® tablet:

Do not take the tablet within 3 hours of a meal. It may not work as well, or it might make you sleepy the next day.

Take the tablet 30 minutes before you go to bed.

Do not take the medicine unless you can get a full night's sleep (7 to 8 hours).

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 [doxepin](#) works. Tell your doctor if you are using any of the following:

[Cimetidine](#), [tolazamide](#)

Other medicines for depression (such as [citalopram](#), [escitalopram](#), [fluoxetine](#), [paroxetine](#), [sertraline](#)), a phenothiazine medicine (such as [chlorpromazine](#), [perphenazine](#), [promethazine](#), [prochlorperazine](#), [thioridazine](#)), or medicines for heart rhythm problems (such as [flecainide](#), [propafenone](#), [quinidine](#))

Do not drink alcohol while you are using this medicine.

This medicine can intensify the effects of other medicine that makes you sleepy, such as allergy medicine and narcotic pain medicine.

**Warnings While Using This Medicine:**

Tell your doctor if you are pregnant or breastfeeding, or if you have liver disease, problems urinating, [glaucoma](#), [sleep apnea](#), or a history of mental illness.

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

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

Silenor® tablets may cause you to do things while you are still asleep that you may not remember the next morning, such as driving a car, having sex, or eating food. Tell your doctor right away if you learn that this has happened.

This medicine may make you drowsy. Do not drive or do anything that could be dangerous until you know how this medicine affects you.

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

Silenor® tablets: Call your doctor if you still have trouble sleeping after you take this medicine for 7 to 10 days.

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

Changes in behavior, or thoughts of hurting yourself or others

Eye pain, vision changes, seeing halos around lights

Fast, pounding, or uneven heartbeat

Feeling nervous, restless, anxious, agitated, or excited for no reason

Seizures or tremors

Severe confusion, or seeing or hearing things that are not there

Unusual bleeding or bruising

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

Constipation

Dizziness or drowsiness

Dry mouth

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

**B)) Doxepin** (On the skin)

**Doxepin**

Reduces itching caused by skin diseases such as [atopic dermatitis](#) or [lichen simplex chronicus](#).

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an [allergic reaction](#) to [doxepin](#), or if you have [glaucoma](#) or problems urinating.

How to Use This Medicine:

Cream

Apply a thin layer of the medicine to the affected area. Rub it in gently.

Apply a thin layer of this medicine each time you use it.

Wash your hands with soap and water before and after you use this medicine.

Do not cover the treated area with a bandage unless directed by your doctor.

If a Dose is Missed:

Apply a dose as soon as you can. If it is almost time for your next dose, wait until then and apply a regular dose. Do not apply extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist or doctor how to dispose of the medicine container and any leftover or expired medicine.

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

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are using MAO inhibitors such as [Eldepryl®](#), [Marplan®](#), [Nardil®](#), or [Parnate®](#), or allergy medicines.

Make sure your doctor knows if you are using medicine for depression such as trazadone, Clexa®, [Prozac®](#), [Paxil®](#), or [Zoloft®](#), or [amitriptyline](#), [Norpramin®](#), or [Vivactil®](#).

There are many other drugs that can interact with [doxepin](#). Make sure your doctor knows about all other medicines you are using.

Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breast feeding.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

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  
Confusion, hallucinations, severe weakness, vomiting, muscle stiffness.  
Drowsiness or lightheadedness or fainting.  
Irregular heartbeat  
Swelling in your feet, arms, or body.

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

Burning or stinging of your skin where the medicine is applied.  
Change in taste or dryness of your mouth.  
Headache or tiredness.  
Nervousness, anxiety.  
Numbness in your tongue.  
Redness, pain, swelling, or itching on site of cream application.  
Worsening of your skin condition.

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

#### 4.3] Place In Therapy

##### A) Doxepin Hydrochloride

###### 1) Anxiety and/or Depression

a) Doxepin hydrochloride capsules are indicated for the treatment of depression and/or anxiety in patients with psychoneurotic symptoms, alcoholism, or organic disease. Doxepin is also indicated for the treatment of psychotic depressive disorders associated with anxiety including involuntary depression and manic-depressive disorders [218].

b) Depression is a complicated disorder and consequently treatment regimens are diverse. The two most prevalent diagnostic syndromes among affective disorders are major depression and bipolar disorders. The tricyclic antidepressants (TCAs), serotonin reuptake inhibitors (SSRIs) 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, SSRIs, and other agents such as carbamazepine or levothyroxine.

c) Doxepin is effective for the treatment of endogenous or typical depression. Doxepin has similar efficacy and adverse effects as the other TCAs, but possesses some distinguishing characteristics. Doxepin inhibits histamine release and has been used topically to treat pruritus and systemically for peptic ulcer disease. Doxepin has also been used for treating anxiety-depression states and depression-induced insomnia. Cardiac effects of doxepin are considered mild compared to those of the other TCAs.

d) Doxepin does have a place in therapy for the treatment of unipolar depression, but should be considered secondary to imipramine and amitriptyline. Because of anxiolytic properties, antihistamine action, sedative effects and fewer cardiac effects, doxepin may be useful for treating depressed patients with co-anxiety, peptic ulcer disease, associated insomnia, or who are elderly.

###### 2) Insomnia



a)] **Doxepin** hydrochloride tablets (Silenor(R)) are indicated for the treatment of insomnia characterized by difficulties with sleep maintenance [22].

### 3)] Pruritus

a)] **Doxepin** hydrochloride 5% cream (**Zonalon(R)**) is indicated for the short-term management of moderate **pruritus** in adult patients with **eczematous dermatitis** (ie, **atopic dermatitis**, **lichen simplex chronicus**) [44].

## 4.4] Mechanism of Action / Pharmacology

### A)] **Doxepin** Hydrochloride

#### 1)] Mechanism of Action

a)] **Doxepin** hydrochloride belongs to a class of psychotherapeutic agents called dibenzoxepin tricyclic compounds [42][44][22], and possess pharmacologic properties similar to other tricyclic antidepressants [779]. Its exact mechanism of action is unknown. Animal studies have demonstrated anticholinergic, antiserotonin and antihistamine effects on smooth muscle [42]. **Doxepin** hydrochloride may produce prominent cardiovascular effects as a result of its anticholinergic activity on the heart and a "quinidine-like" myocardial depressant action, as well as inhibition of **norepinephrine** uptake at adrenergic synapses. [784][785][786][787]

#### 1)] Depression

a)] The antidepressant effect of doxepin hydrochloride is believed to be partly due to its influences on the adrenergic activity at the synapses where it prevents norepinephrine deactivation through reuptake into the nerve terminals [42]. It has similar pharmacologic properties to other tricyclic antidepressants. Doxepin hydrochloride has a pronounced sedative effect similar to amitriptyline but probably less than that of imipramine. It is particularly effective in depression associated with anxiety or in mixed anxiety depression syndromes [779]. Doxepin hydrochloride may be more effective than imipramine in patients with depression associated with sleep disturbances but it is not superior to other tricyclic antidepressants for severe endogenous depression [779]

#### 2)] Pruritus

a)] The antipruritic effect of doxepin hydrochloride is believed to be due to its potent H1 and H2 receptor blocking action. It competes at histamine receptor sites to inhibit the activation of histamine receptors. Significant plasma levels of doxepin are achieved following topical administration. In 19 pruritic eczema patients treated with topical doxepin hydrochloride 5% cream, doxepin concentrations ranged from nondetectable to 47 nanograms/mL. Because a significant number of patients treated with doxepin hydrochloride experience sedation, it appears sedation may also have an effect on certain pruritic symptoms [44].

#### 3)] Sleep Maintenance

a) The most likely mechanism by which doxepin hydrochloride exerts its sleep maintenance effect is its antagonism of the histamine H1 receptor [22].

## 4.5] Therapeutic Uses

### 4.5.1] FDA Uses

#### 4.5.1.A] Doxepin Hydrochloride

##### 4.5.1.A.1] Alcoholism - Anxiety - Depression

FDA Labeled Indication

##### a) Overview

FDA Approval: Adult, yes (oral capsule and concentrate); Pediatric, yes (12 years or older, oral capsule and concentrate)

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### b) Summary: Indication

[Doxepin](#) is indicated for anxiety and depression associated with alcoholism [2][3].

Evidence

[Doxepin](#) was significantly more effective than [diazepam](#) in reducing symptoms of anxiety, depressed mood, somatization, guilt, and tension in a randomized 3-week trial in men admitted for inpatient alcohol treatment with concurrent anxiety and depression (N=39) [12].

##### 4.5.1.A.2] Anxiety

FDA Labeled Indication

##### a) Overview

FDA Approval: Adult, yes (oral capsule and concentrate); Pediatric, yes (12 years or older, oral capsule and concentrate)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### b) Summary: Indication

[Doxepin](#) is indicated for the treatment of anxiety, with or without depression, in psychoneurotic patients or those with organic disease [2][3].

#### Evidence

[Doxepin](#) significantly improved symptoms of anxiety compared with placebo and symptoms associated with anxiety, guilt, depression, and anger compared with [chlorthalidone](#) at 4 weeks in a randomized trial in outpatients with mixed anxiety and depression (N=121) [4]. Similar significant reductions in symptoms of anxiety, depression, and tension were observed in comparison with [diazepam](#) at 8 weeks in a randomized trial of outpatients with mixed anxiety, depression, and tension (N=47), but [doxepin](#) was associated significant increases in weight (3 kg vs 0 kg) [5].

#### 4.5.1.A.3] Depression

##### FDA Labeled Indication

###### a) Overview

FDA Approval: Adult, yes (oral capsule and concentrate); [Pediatric, yes \(12 years or older, oral capsule and concentrate\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

###### b) Summary:

##### Indication

[Doxepin](#) is indicated for the treatment of depression, with or without anxiety, in psychoneurotic patients or those with organic disease [2][3].

#### Evidence

[Doxepin](#) significantly improved symptoms of anxiety compared with placebo and symptoms associated with anxiety, guilt, depression, and anger compared with [chlorthalidone](#) at 4 weeks in a randomized trial in outpatients with mixed anxiety and depression (N=121) [4]. Similar significant reductions in symptoms of anxiety, depression, and tension were observed in comparison with [diazepam](#) at 8 weeks in a randomized trial of outpatients with mixed anxiety, depression, and tension (N=47), but [doxepin](#) was associated significant increases in weight (3 kg vs 0 kg) [5].

#### 4.5.1.A.4] Depression - Psychotic disorder

##### FDA Labeled Indication

###### a) Overview

FDA Approval: Adult, yes (oral capsule and concentrate); [Pediatric, yes \(12 years or older, oral capsule and concentrate\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

**Indication**

[Doxepin](#) is indicated for the treatment of psychotic [depressive disorders](#) with associated anxiety, including [involutional depression](#) and [manic-depressive disorders](#) [2][3].

**Evidence**

[Doxepin](#) significantly improved symptoms of anxiety compared with placebo and symptoms associated with anxiety, guilt, depression, and anger compared with [chlordiazepoxide](#) at 4 weeks in a randomized trial in outpatients with mixed anxiety and depression (N=121) [4]. Similar significant reductions in symptoms of anxiety, depression, and tension were observed in comparison with [diazepam](#) at 8 weeks in a randomized trial of outpatients with mixed anxiety, depression, and tension (N=47), but [doxepin](#) was associated significant increases in weight (3 kg vs 0 kg) [5].

**4.5.1.A.5] Insomnia, Characterized by difficulty with sleep maintenance**

**FDA Labeled Indication**

**a) Overview**

FDA Approval: Adult, yes (Silenor(R) only); **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

**Indication**

[Doxepin](#) hydrochloride (Silenor(R)) is indicated for the treatment of insomnia characterized by difficulties with sleep maintenance [22].

**Evidence**

[Doxepin](#) 3 mg and 6 mg improved subjective and objective reports of time awake after sleep onset, compared with placebo, across 6 randomized trials in adults lasting up to 3 months (N=1423). Among included patients, 858 had insomnia of at least 3 months duration, 565 had transient insomnia during a one-night sleep laboratory evaluation, and 494 were elderly (up to 93 years) [22]. In 2 similar studies, [doxepin](#) 3 and 6 mg significantly reduced objective wake time during sleep (WTDS), reduced wake time after sleep onset, improved total sleep time, and improved overall sleep efficiency compared with placebo in 76 elderly patients (mean age, 71 years) [23] and significantly reduced objective WTDS (3 mg, 34 min and 6 mg, 35.8 min vs 51.5 min) and improved sleep efficiency (86.5% and 87.2% vs 81.2%) compared with placebo in non-elderly adults (N=67) [24].

**4.5.1.A.6] Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus**

## FDA Labeled Indication

## a) Overview

FDA Approval: Adult, yes (5% cream); **Pediatric, no**

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

## b) Summary:

## Indication

[Doxepin](#) 5% cream is indicated for short-term management (no more than 8 days) of [pruritus](#) in patients with [atopic dermatitis](#) or [lichen simplex chronicus](#) [39].

Safety and effectiveness have not been evaluated for greater than 8 days of use and may result in higher systemic levels or increased likelihood of contact sensitization [39]

## Evidence

Topical [doxepin](#) provided relief to a significantly higher proportion of patients compared with placebo (85% vs 57%) in a 7-day randomized trial in patients with [atopic dermatitis](#) (N=270). Drowsiness occurred more often with [doxepin](#) (37 vs 3 patients) although severity decreased with duration of use [41].

The addition of [doxepin](#) to topical corticosteroids significantly improved [pruritus](#) severity in a randomized trial of patients with pruritic [atopic dermatitis](#) (N=349). Patients applied [doxepin](#) 5% with [hydrocortisone](#) 2.5% or [triamcinolone](#) 0.1%, or either steroid as monotherapy, 4 times daily for 8 days. [Pruritus](#) severity was significantly reduced with both [doxepin](#) combinations at 12 hours (31.6% and 22.4% vs 8% and 10.7%) and on day 2 (70.4% and 79.1% vs 46.7% and 66.7%). More patients experience mild, transient drowsiness with combination therapy (38% and 10% vs 9% and 5%) [40].

## 4.5.2] Non FDA Uses

4.5.2.A] [Doxepin](#) Hydrochloride4.5.2.A.1] [Cancer](#) pain

## a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

## b) Summary:

Case reports have described the use of [doxepin](#) in terminal [cancer](#) patients who are unresponsive to narcotic analgesics

See Drug Consult reference: Management of Cancer-Related Pain in Adult Patients

**c) Adult:**

**1)** Four severely debilitated **cancer** patients with neuropathic pain were reported to be more comfortable following rectal administration of unmodified **DOXEPIN** capsules. Serum concentrations of N-desmethyldoxepin after two to five days of treatment with a constant dose of **DOXEPIN** were 573 micrograms/milliliter (mcg/mL) and 403 mcg/mL (with 50 milligrams (mg) three times/day), 204 mcg/mL (with 50 mg twice a day), and less than 25 mcg/mL (with 25 mg every day) [10].

**2)** The combination of **PIROXICAM** (60 to 120 milligrams orally daily, given with **SUCRALFATE** 1 to 2 grams daily) plus **DOXEPIN** (25 to 225 mg daily) was reported effective in the treatment of **advanced cancer** pain [11]. **SUCRALFATE** given concurrently with **PIROXICAM** was effective in preventing severe gastrointestinal (GI) toxicity. However, several patients did not administer **sucralfate** concurrently with **PIROXICAM** and developed GI symptoms (**GI hemorrhage**, **gastric ulcer** or perforation). It is recommended that **PIROXICAM** and **DOXEPIN** therapy (with adjunctive **SUCRALFATE** administration) be considered in patients with terminal **cancer** who are unresponsive to narcotic analgesics.

**4.5.2.A.2] Cocaine-induced anxiety disorder**

**a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

**b) Summary:**

Not effective in the treatment of panic attacks associated with cocaine abuse

**c) Adult:**

**1)** The use of tricyclic antidepressant therapy in 10 patients with cocaine-induced panic attacks resulted in extreme anxiety and had to be discontinued [27]. One patient improved after **doxepin** 50 milligrams/day (mg/day) but, at higher doses, became severely confused and panicky and had to be hospitalized. Another patient had a partial response to **trazodone** 150 mg/day and did not want to be switched to another agent. Other agents used in this patient population included **amitriptyline**, **desipramine**, and **nortriptyline**. Thus, heterocyclic antidepressants were not well tolerated except for **trazodone** and low doses of **doxepin**, two medications with relatively high serotonergic re-uptake blockade.

**4.5.2.A.3] Complex regional pain syndrome**

**a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive



Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Topical [doxepin](#) reduced the symptoms of [complex regional pain syndrome](#) CRPS, including pain, discoloration, and thermal and mechanical allodynia

**c) Adult:**

**1)** A 32-year-old woman attained relief of symptoms of [complex regional pain syndrome](#) (CRPS) with topical application of [doxepin](#) 5% cream (Xepin(R)). After a fall on her left wrist, the woman developed the symptoms of CRPS, although the wrist was not broken. In addition to burning dermatomal pain, she showed blue discoloration, hyperhidrosis, and mechanical and thermal allodynia. A [stellate ganglion block](#) on the left side gave significant reduction in symptoms for 4 weeks. A second block provided similar relief. Topical application of [doxepin](#) cream twice daily reduced her symptoms significantly after 2 weeks. Each time she omitted using the cream for more than 5 days, her symptoms returned. In addition to reducing the pain, it decreased the thermal and mechanical allodynia and the discoloration [13].

**4.5.2.A.4] Cyclical vomiting syndrome**

**a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Tricyclic antidepressant therapy, including [DOXEPIN](#), may be beneficial in treating CYCLIC VOMITING SYNDROME

**c) Adult:**

**1)** In a retrospective case series (n=17), adults with CYCLIC VOMITING SYNDROME (CVS) were shown to derive benefit from treatment with low-dose tricyclic antidepressants (open-label), including [DOXEPIN](#) (median dose 50 milligrams (mg) daily; range 25 to 150 mg). However, a comparison group of 37 patients with usual functional nausea and vomiting had superior results from tricyclic-antidepressant therapy compared with those with CVS. Of the 17 patients with CVS, 3 (17.6%) achieved complete remission, and 10 (58.8%) attained partial response (decreased intensity of symptoms, decreased cycle frequency, or shortening of cycles). Of 7 patients who used [doxepin](#), 6 experienced remission or improvement -- the same response as 7 patients given [amitriptyline](#). No patient responded to [desipramine](#) (0 of 3) or [imipramine](#) (0 of 1), with 4 of 4 responding to [nortriptyline](#). Of the patients with functional nausea and vomiting treated with tricyclic antidepressants, 19 of 37 (51.4%)

achieved complete remission and 12 (32.4%) showed partial response. The authors suggest that the pathophysiology of CVS might be similar to that of migraine headache [38].

#### **4.5.2.A.5] Depression - Opioid dependence**

##### **a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### **b) Summary:**

**DOXEPIN** reduced the craving for HEROIN, nervousness, and the use of **amphetamines**

##### **c) Adult:**

1) **Doxepin** was superior in the treatment of depression when compared with placebo in a 5-week trial as adjunctive treatment in a **methadone maintenance** program. Only 46 of 76 patients completed the study. Relative to several depression parameters, **doxepin** was shown better than placebo. **Doxepin** did not significantly increase the incidence or severity of adverse effects to **methadone** [14]

2) **DOXEPIN** was efficacious in HEROIN addicts with associated anxiety and depression. Doses of 100 to 150 mg daily for periods of longer than 4 weeks significantly decreased symptoms of anxiety and depression as measured by the Hamilton depression rating scale [15].

#### **4.5.2.A.6] Detrusor instability of bladder**

##### **a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### **b) Summary:**

Effective in the treatment of detrusor overactivity in women

##### **c) Adult:**

1) **DOXEPIN** caused a significant decrease in the nighttime micturition frequency and the nighttime incontinence episodes. Cystometric parameters improved significantly during treatment with **DOXEPIN**. The authors concluded that **DOXEPIN** seems to offer a new alternative in the **pharmacological treatment** of detrusor overactivity and associated symptoms [16].

2j) In this randomized, double-blind, placebo-controlled study of DOXEPIN, 19 females with detrusor overactivity and associated symptoms who had failed to respond to conventional pharmacotherapy, obtained relief ascribed to the ability of DOXEPIN to improve storage failure by decreasing bladder contractility and/or decreasing sensory input [16]. DOXEPIN caused a significant decrease in the nighttime micturition frequency and the nighttime incontinence episodes (p less than 0.05). Cystometric parameters improved significantly during treatment with DOXEPIN. The authors concluded that DOXEPIN seems to offer a new alternative in the pharmacological treatment of detrusor overactivity and associated symptoms.

#### 4.5.2.A.7] Disorder of gastrointestinal tract

##### a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

An effective alternative in treating IRRITABLE BOWEL SYNDROME

Other types of epigastric distress have also reportedly responded to therapy

##### c) Adult:

1j) A meta-analysis of controlled clinical trials related to the use of antidepressants for the treatment of functional gastrointestinal (GI) disorders concluded that this type of therapy (primarily tricyclic antidepressants) is efficacious in some patients. Included were 11 trials published between 1978 and 1998 focused on antidepressant therapy in irritable bowel syndrome (8) and dyspepsia (non-ulcer) (2); one study included patients with either disorder. Among the medications studied were amitriptyline (3), trimipramine (3), desipramine (2), DOXEPIN (1), mianserin (1), and either clomipramine or mianserin (1). All of the trials compared the treatment drug against placebo. In 8 studies using a dichotomous outcome measure, ie, response to treatment, the odds ratio for improvement with therapy was 4.2. In 7 studies using a continuous variable of pain scores, the standardized mean improvement in pain averaged 0.9 standard deviation (SD) (means for the treatment and control groups divided by the SD). Pooling of the risk difference indicated that 3.2 patients needed to be treated for 1 to experience symptom improvement. The authors were uncertain if the improvement in GI symptoms was an independent action of the drugs or if the improvement reflected the effects of the drugs on the psychological outlook of the recipients [17].

2j) A nondepressed patient obtained relief from irritable bowel syndrome, resistant to other therapies, while receiving DOXEPIN 150 milligrams/day [18]. Another similar case with similar results was reported [19].

3j) Doxepin relieved 2 cases of epigastric distress [20]. A 77-year-old man with an 8-year history of severe, unremitting epigastric distress experienced significant relief on DOXEPIN

100 milligrams/day. Similar results were observed in a 55-year-old man after initiation of [DOXEPIN](#) 125 milligrams/day.

#### **4.5.2.A.8] Disorder of oral mucous membrane - Pain**

##### **a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### **b) Summary:**

Mucosal local [doxepin](#) rinse relieved mucosal pain caused by [cancer](#) or [cancer](#) treatment for more than 3 hours

##### **c) Adult:**

1) An oral rinse of [doxepin](#) solution gave relief of pain to patients with oral mucosal damage. In a single-dose, open trial, 41 patients with oral mucosal pain resulting from [cancer](#) or [cancer](#) treatment rinsed their mouths for 1 minute with 5 milliliters (mL) of [doxepin](#) suspension 5 milligrams/mL. At 15 minutes post-rinsing, mean pain reduction was 60% (p less than 0.01), and at 3 hours, 25% (p less than 0.05). By 24 hours, pain had returned to pre-rinse levels. Thirty-five percent of patients reported absence of fatigue, 13% mild fatigue, 20% moderate, 16% moderate-to-severe, and 16% severe [25].

#### **4.5.2.A.9] Nicotine dependence**

##### **a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### **b) Summary:**

[Doxepin](#) may be a useful adjunct in smoking cessation

##### **c) Adult:**

1) [DOXEPIN](#) was efficacious in the treatment of NICOTINE WITHDRAWAL (Edwards et al, 1990). [DOXEPIN](#) was given to 8 patients prior to smoking cessation with the following regimen: 25 milligrams at bedtime initially and titrated in increments of 25 milligrams every third day to reach a target dose of 150 milligrams. When 150 milligrams/day was maintained for 1 week, patients were instructed to terminate smoking. Twenty-one patients were instructed to begin smoking cessation after the initial visit. Dropouts were more frequent

in the patients that did not receive DOXEPIN (72% compared with 50% in the DOXEPIN patients). DOXEPIN significantly suppressed symptom frequency during the first and second week as compared with the patients who did not receive DOXEPIN.

2) A 5-week pilot study revealed that DOXEPIN therapy was useful in nicotine withdrawal [35]. Of the original 8 subjects treated with DOXEPIN and 21 controls, only 4 of the DOXEPIN group and 6 controls finished the study. DOXEPIN reduced the severity of symptoms during the first 2 weeks but there was no significant difference in the last 3 weeks.

3) DOXEPIN was reported effective in achieving smoking cessation in a small double-blind study involving 19 adults [36][37]. Prior to smoking cessation, the DOXEPIN (or placebo) was given in doses of 50 milligrams daily for 3 days, then 100 milligrams daily on days 4 through 6, followed by 150 milligrams daily from day 7 to 21. On day 22, subjects stopped smoking and DOXEPIN 150 milligrams daily or placebo was continued for an additional 4 weeks. The study medication was given at bedtime. Smoking cessation was achieved in all of the 9 subjects treated with DOXEPIN 7 days after stopping smoking and was maintained in 7 of the subjects at 9 weeks; only 1 of 10 placebo subjects reported cessation. A pre-cessation DOXEPIN serum level higher than 10 ng/mL was associated with cessation of smoking in this study. In the 2 DOXEPIN subjects reporting relapse, DOXEPIN levels were less than 10 ng/mL. DOXEPIN appeared to reduce the intensity of cigarette craving (2.8 +/- 1.7 for DOXEPIN users versus 5.1 +/- 0.8 for placebo). Substantial weight gain was observed in subjects treated with DOXEPIN who were able to stop smoking (mean, 5.3 kg). It is suggested that the weight gain attributable to cessation of smoking was most likely compounded by weight gain secondary to DOXEPIN use. This small study suggests that DOXEPIN may have a role in assisting smoking cessation.

#### 4.5.2.A.10] Pain, chronic

##### a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Patients with chronic pain have experienced some relief with doxepin therapy

A review of doxepin as adjunctive therapy for chronic pain has been published by the Boston Pain Center (Aronoff & Evans, 1982)

##### c) Adult:

1) DOXEPIN (up to 3 milligrams/kilogram/day (mg/kg)) for pain relief was better than placebo in 60 patients with chronic low back or cervical pain and depression [26]. Relative to the percent of time the pain was felt, effect of pain on sleep, and muscle tension, DOXEPIN was slightly better than placebo at 1 week, and significantly better at 6 weeks. Benefit was most consistently derived when the daily dose was at least 2.5 mg/kg, and the combined

DOXEPIN/desmethylloxepin plasma level exceeded 70 ng/mL. The proposed mechanism, as demonstrated by the laboratory, was enhanced enkephalin activity.

#### 4.5.2.A.11] Peptic ulcer disease

##### a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Effective in the treatment of peptic ulcer disease due to its histamine blocking activity

##### c) Adult:

1) Tricyclic antidepressants have anti-histamine blocking properties, however, standard H<sub>2</sub> antagonists are recommended for the treatment of peptic ulcer disease. For peptic ulcer disease, doxepin has been as effective as cimetidine [28][29][30] and doxepin was effective in patients who had failed cimetidine [28][31].

2) Doxepin was superior to placebo in a study of the effect of doxepin on gastric acid and salivary secretion in patients with asymptomatic, chronic duodenal ulcer disease. Seven patients received either 50 or 100 milligrams doxepin or placebo, and were evaluated at 3.5, 5.5, 7.5, and 9.5 hours after drug administration. Both gastric acid and salivary secretion were decreased significantly more by doxepin than placebo, but no statistically significant differences were seen between the 2 doses of doxepin [32].

#### 4.5.2.A.12] Post-prandial hypoglycemia

##### a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Has reduced symptoms of postprandial symptomatic hypoglycemic.

##### c) Adult:

1) DOXEPIN reduced symptoms of postprandial symptomatic hypoglycemic in 32 subjects [33]. There was a 4-week baseline period followed by an 8-week study with DOXEPIN 25 milligrams being substituted for placebo. During the placebo period, all patients showed



hypoglycemia, hyperinsulinemia, and disorders of plasma neurotransmitters during the oral glucose tolerance test when compared with control subjects. The subjects were divided into 3 separate groups according to different blood levels of neurotransmitters. Groups I and II showed low basal noradrenalin/adrenalin ratios and low serotonin levels. Group III had a high noradrenalin/adrenalin ratio with a raised serotonin level and all subjects showed severe dysthymic depression. The symptoms of postprandial hypoglycemia did not correlate with a low glucose level but rather an imbalance in the neurotransmitter levels. Serotonin and noradrenalin stimulate hypothalamic activity which reduces pituitary-adrenocortical functioning. This in turn reduces the adrenaline level and causes hypoglycemia. All 32 subjects showed pituitary-adrenocortical hyperactivity before treatment. After treatment with DOXEPIN they were all asymptomatic.

#### 4.5.2.A.13] Posttraumatic stress disorder

##### a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Tricyclic antidepressant therapy including doxepin has been reported beneficial in the treatment of posttraumatic stress disorder in COMBAT VETERANS (Falcon et al, 1985)

##### c) Adult:

1) Posttraumatic stress disorder due to trauma, burns, rape, and other noncombat physical insults have been treated with antidepressants. A 36-year-old male suffered posttraumatic stress disorder several months after receiving second and third degree burns in a truck fire. The patient responded well to DOXEPIN (daily doses of 50 milligrams (mg) to start, increasing to 300 mg, then tapering to 50 mg) over a period of 1 year [34].

#### 4.5.2.A.14] Psychogenic headache

##### a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Beneficial results of DOXEPIN have been reported in patients with PSYCHOGENIC HEADACHE

## c) Adult:

1) Beneficial results of DOXEPIN were reported in patients with PSYCHOGENIC HEADACHE following anxiety/depressive illnesses [21]. Doses of 10 milligrams three times/day were administered and dosage increased when required by 2 mg daily after 2 weeks at weekly intervals. The study lasted 8 weeks, and by the fourth week the majority of patients noticed marked improvement. When compared with AMITRIPTYLINE and DIAZEPAM, DOXEPIN was the only drug with a highly significant effect on headache, anxiety, and depression. The investigators speculate that superiority of DOXEPIN may be attributed to its effect as an antianxiety agent, antidepressant, and central muscle relaxant.

## 4.5.2.A.15] Urticaria

## a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

## b) Summary:

Effective in the treatment of urticaria

## c) Adult:

1) Oral DOXEPIN 10 to 30 milligrams daily has been effective in the treatment of IDIOPATHIC COLD URTICARIA, effectively suppressing the wheal and itching responses and shortening the duration of the wheal response in the ice cube test [6].

2) Oral DOXEPIN 5 milligrams twice a day was effective in the treatment of chronic idiopathic URTICARIA in a controlled study. Oral MEQUITAZINE (a phenothiazine antihistamine) 5 mg twice a day was equally effective [7][8].

3) Oral DOXEPIN 25 milligrams three times a day was effective in the treatment of CHRONIC IDIOPATHIC URTICARIA in a placebo-controlled trial involving 16 adult patients [9]. Patients were randomly assigned to receive either DOXEPIN or placebo for 4 weeks; each group was then crossed over for the next 4 weeks. DOXEPIN was associated with fewer waking hours with lesions, and less angioedema and swelling as compared to placebo-treated patients. Daily antihistamine use was less in patients treated with DOXEPIN. Lethargy was observed during DOXEPIN therapy but decreased with continued use of the drug; dry mouth and constipation were also reported.

## 4.6] Comparative Efficacy / Evaluation With Other Therapies

## 4.6.A] Amitriptyline

## 4.6.A.1] Depression

a) Clinical studies have shown that doxepin and amitriptyline are of comparable efficacy in depression; side effects have occurred with greater frequency in patients receiving amitriptyline [832][833][834].

b) In one study, [amitriptyline-perphenazine](#) produced significantly greater improvement than [doxepin](#) on several measures of psychiatric tests. The combination also produced a greater incidence of sedation and anticholinergic side effects [835]. [Doxepin](#) 100 to 150 milligrams/day was compared with a combination of [amitriptyline](#) 100 to 150 milligrams/day plus [perphenazine](#) 8 to 12 milligrams/day in 130 depressed, nonpsychotic outpatients over a period of 4 weeks.

c) Four antidepressants were used in a group of 116 private practice patients suffering from depression associated with chronic or recurrent pain. Dosage range was 150 to 300 milligrams/day, and the antidepressant was changed if necessary to get an adequate response. The response to the 4 antidepressants was not statistically significantly different: [doxepin](#) 17 of 22 (77%); [imipramine](#) 33 of 44 (75%); [amitriptyline](#) 21 of 25 (84%); and [desipramine](#) 34 of 44 (75%). A significant response was a 50% reduction in pain judged subjectively [836].

d) [Doxepin](#) was compared with [amitriptyline](#) in acutely depressed patients using cortical evoked potentials as the measurement of success [837]. Many depressed patients have a magnified perception of intensity to a stimulus; thus, often they complain of pain which to others might be described as discomfort. In 33 patients, baseline potentials were measured after 1 week of placebo therapy, then they received 150 milligrams/day of either [doxepin](#) or [amitriptyline](#). Five visual and 5 auditory evoked potentials were recorded. [Doxepin](#) reduced the amplitudes of the evoked potentials significantly. [Amitriptyline](#) had a similar, but insignificant effect.

e) One author reported that [doxepin](#) showed faster pharmacologic activity and greater antidepressive and anxiolytic effects than [amitriptyline](#) [834].

#### 4.6.B] Amitriptylinoxide

##### 4.6.B.1] Depression

a) [Doxepin](#) and amitriptylinoxide, in doses of 180 to 360 milligrams/day, had a similar efficacy in a four-week study involving 44 inpatients with severe depression. Efficacy was judged on several rating scales. The two drugs showed comparable efficacy and there were no significant differences in adverse effects [827].

#### 4.6.C] Amoxapine

##### 4.6.C.1] Mixed anxiety and depressive disorder

a) [Amoxapine](#) 160 milligrams/day (maximum dose) was compared with [doxepin](#) 130 milligrams/day (maximum dose) in the treatment of mixed anxiety/depression in 142 patients. Twenty-four to 31 of amoxapine-treated subjects (n=71) and 16 to 24 of doxepin-treated subjects (n=71) receiving [doxepin](#) were identified as improved after 4 weeks. [Amoxapine](#) achieved a more rapid response. Side effects between the 2 treatments were comparable; however, [doxepin](#) caused more constipation [817].

#### 4.6.D] Bupropion

##### 4.6.D.1] Depression

a) [BuPROPion](#) 300 to 450 milligrams daily was reported similar in efficacy to [doxepin](#) 100 to 225 milligrams daily in the treatment of [major depressive disorder](#) in a double-blind study involving 147 outpatients [818]. [Doxepin](#), however, improved sleep better than [buPROPion](#); anticholinergic side effects were more frequent with [doxepin](#) as compared with [buPROPion](#), as was increased appetite and weight gain.

#### 4.6.E] Capsaicin

##### 4.6.E.1] Neuropathic pain - Pain, chronic

a) Topical [doxepin](#) hydrochloride, topical [capsaicin](#), or the combination of the 2 all provided analgesia in chronic human neuropathic pain (CNP), in contrast to placebo. In a randomized, double-blind, placebo-controlled trial, 200 patients with CNP were given placebo cream, 3.3% [doxepin](#) hydrochloride cream, 0.25% [capsaicin](#) cream, or a cream containing 3.3% [doxepin](#) and 0.25% [capsaicin](#). Patients were to apply a volume of cream approximately equal in size to a grain of rice 3 times daily to the painful area for 4 weeks. Overall pain was unchanged in the placebo group. In the other 3 groups, overall pain decreased from approximately 7 to approximately 6 on a pain scale ranging from 0 to 10 (p less than 0.001 for all drug groups). Scores for burning pain were unchanged in the placebo group but increased in all 3 drug groups at week 1 and, though diminishing somewhat thereafter, remained significantly above that of the placebo group. Sensitivity was unchanged by placebo and [doxepin](#) but declined significantly, beginning in the first week, with both [capsaicin](#) (p less than 0.001) and [doxepin/capsaicin](#) (p less than 0.01) treatments. Shooting pain was reduced by the [capsaicin](#) treatments but not by [doxepin](#) or placebo. Ten percent of patients in the [doxepin](#) group and 5% in the [doxepin/capsaicin](#) group complained of drowsiness, suggesting the systemic absorption of [doxepin](#). A burning sensation was reported by 81% of those in the [capsaicin](#) and by 61% of those in the [doxepin/capsaicin](#) group [798].

#### 4.6.F] [Chlordiazepoxide](#)

##### 4.6.F.1] [Anxiety](#)

a) Most clinical studies to date have indicated that [doxepin](#) has proven as useful as [chlordiazepoxide](#) in patients with [anxiety neurosis](#) [819][820][821]. At this point [doxepin](#) can not be recommended over [chlordiazepoxide](#) or other benzodiazepines in neurotic anxiety but is recommended as the drug of choice in patients with mixed anxiety-depression states [822].

#### 4.6.G] [Cimetidine](#)

##### 4.6.G.1] [Duodenal ulcer disease](#)

a) In a double-blind randomized study of 21 patients, [doxepin](#) (50 milligrams at bedtime for 1 week, followed by 100 milligrams at bedtime) was comparable with [cimetidine](#) 300 milligrams four times a day for the treatment of [duodenal ulcers](#) [796]. After 6 weeks, the average ulcer size decreased by 97% in both groups. Interestingly, [doxepin](#) was significantly more effective in women than in men, while [cimetidine](#) was more effective in men than in women. Further large studies are needed to confirm whether there truly exists a sex-related difference in [ulcer healing](#), especially with [doxepin](#).

#### 4.6.H] [Cinnarizine](#)

##### 4.6.H.1] [Urticaria](#)

a) A randomized, double-blind, crossover trial in 10 patients with primary acquired [idiopathic cold urticaria](#) compared the effects of cinnarizine 10 milligrams (mg) three times daily with [doxepin](#) 10 mg three times daily and placebo. Each arm of therapy lasted two weeks. Eight patients considered [doxepin](#) superior to cinnarizine. Cinnarizine provided some symptom relief in five patients, and was ineffective in four. One patient discontinued cinnarizine therapy due to excessive fatigue. Placebo produced no symptom relief [797].

#### 4.6.I] [Clomipramine](#)

##### 4.6.I.1] [Dysthymia](#)

a) Results were equivocal in a study that compared [clomiPRAMINE](#) and [doxepin](#) (75 milligrams/day of either) in a group of 66 patients with [neurotic depression](#). Patient-rated measures did not show a

superior agent. **ClomiPRAMINE** was rated better by physician-rated measures. There were no significant differences in side effects [788].

**b)** **Doxepin** (25 milligrams three times a day) and **clomiPRAMINE** (25 milligrams three times a day), were more effective than L-tryptophan (500 mg three times a day) in 42 neurotically-depressed patients. The findings of the study were that **doxepin** and **clomiPRAMINE** resulted in more responses than L-tryptophan, therapeutic blood levels of **clomiPRAMINE** and **doxepin** were much smaller than those found in endogenously depressed patients, that responders had a significantly higher blood level of the two than non-responders at 21 days, and that the response to **clomiPRAMINE**, but not **doxepin**, paralleled its accumulation in the blood. [789].

#### 4.6.J] Clovoxamine

##### 4.6.J.1] Depression

**a)** SUMMARY: Clovoxamine offered no clinical advantage over **doxepin** in the treatment of **major depression** in one small double-blind study.

**b)** In a small, double-blind study (n=34), clovoxamine 150 to 300 milligrams daily was generally comparable in efficacy with **doxepin** 75 to 150 milligrams daily in the treatment of **major depression** [795]. However, **doxepin** was statistically superior to clovoxamine with regard to improvement of the anxiety/somatization component of Hamilton Rating Scale for Depression (HAM-D) during the first week of treatment. In addition, patient assessments of the response to treatment were highly in favor of **doxepin**; 97% of doxepin-treated patients indicated they had improved significantly compared to only 50% in the clovoxamine group. Adverse effects were similar in each group, although headache, sweating, and anticholinergic symptoms tended to occur more frequently with clovoxamine. Analysis of pretreatment data in this study indicated more severe depression in the clovoxamine group, which may have influenced results reported. However, several patients with severe **psychotic depression** were also treated effectively with clovoxamine, suggesting efficacy of the drug in this subgroup. A larger and placebo-controlled study comparing these agents is needed.

#### 4.6.K] Desipramine

##### 4.6.K.1] Endogenous depression

**a)** **Doxepin** and **desipramine** were equally effective in a group of 38 patients with a diagnosis of primary affective disorder, **endogenous depression**. Both drugs had equal efficacy, but **doxepin** had a more rapid onset [830].

##### 4.6.K.2] Pain, chronic

**a)** **Desipramine** and **doxepin** had similar efficacy in treating depression and **doxepin** was more effective than **desipramine** in the treatment of pain severity in one study [828]. **Desipramine** (mean dose 173 milligrams/day) was compared with **doxepin** (mean dose 188 milligrams/day) in 36 patients with depression and chronic back pain. Both drugs produced equal responses in depression ratings. Pain severity showed a better response to **doxepin**.

**b)** Four antidepressants had similar efficacy in a group of 116 private practice patients suffering from depression associated with chronic or recurrent pain. Dosage range was 150 to 300 milligrams/day, and the antidepressant was changed if necessary to get an adequate response. The response to the 4 antidepressants was not significantly different: **doxepin** 17 of 22 (77%); **imipramine** 33 of 44 (75%); **amitriptyline** 21 of 25 (84%); and **desipramine** 34 of 44 (75%). A significant response was a 50% reduction in pain subjectively judged [829].

##### 4.6.K.3] Efficacy

a) A prospective study compared oral doses and corresponding plasma levels of [doxepin](#) with [desipramine](#) (as standard reference compound) for 31 patients (19 females, 12 males), mean age 76 (range, 66 to 86). The results in eight doxepin-treated patients (25 to 100 milligrams/day) showed zero levels of [doxepin](#) or its metabolite, desmethyldoxepin, in their plasma. The authors believed that [doxepin's](#) reputation for having fewer side effects may reflect the low plasma levels achieved at commonly prescribed doses and that at more appropriate doses, the side-effect profile may be more in line with standard tricyclics. The authors recommend routine monitoring of [doxepin](#) levels in the elderly and question poor bioavailability or absorption of this tricyclic antidepressant in some patients (Gosselin et al, 1989).

b) [Desipramine](#) suppressed wheal response for 2 days and flare for one day, whereas [doxepin](#) suppressed the wheal for 4 days and flare for 6 days in a double-blind, single dose, noncrossover study. Thirty-three healthy adult volunteers (32 males, 1 female) received a single, oral 25-milligram dose of [desipramine](#) or [doxepin](#). The duration of H1-receptor blockade by these two tricyclic antidepressants were compared. Results showed significant differences in the suppression of the wheal-and-flare responses to [histamine](#) between the two drugs [831]. These results suggest that [doxepin](#) should be withheld for at least 7 days before [allergy skin](#) testing.

#### 4.6.L] [Diazepam](#)

##### 4.6.L.1] Anxiety

a) No significant difference has been observed in clinical trials in patients with anxiety (with or without depression) between [doxepin](#) and [diazepam](#) [5][791][792].

b) A double-blind, placebo-controlled study of 61 outpatients compared [doxepin](#) and [diazepam](#) in the treatment of anxious and anxious-depressive syndromes [793]. After the first week, an enhanced sense of well-being was associated with [diazepam](#). By the end of 6 weeks, there was no significant difference for altering mood and symptomatology with either drug. Objective evaluation rated [diazepam](#) more effective than [doxepin](#) among anxious patients. Drowsiness was the most common side effect. Significant weight gain occurred with [doxepin](#). Possible biases may have been induced by the sampling technique, population characteristics, and consequent drop-out rate.

#### 4.6.M] [Diphenhydramine](#)

##### 4.6.M.1] [Urticaria](#)

a) Oral [doxepin](#) 10 milligrams three times a day was reported significantly superior to oral [diphenhydrAMINE](#) 25 milligrams three times a day in the treatment [chronic idiopathic urticaria](#) in a controlled study involving 50 patients [790]. Clearing of [pruritus](#) and urticarial lesions was observed in 5% and 43% of [diphenhydrAMINE](#) and doxepin-treated patients, respectively; partial or total control [pruritus](#) and hives occurred in 10% and 74% of patients, respectively. [Doxepin](#) was also associated with significantly less sedation than [diphenhydrAMINE](#).

#### 4.6.N] [Dothiepin](#)

##### 4.6.N.1] Depression

a) Dothiepin and [doxepin](#) were similarly effective when administered in single daily doses of 150 milligrams in a ten-week, placebo-controlled, double-blind study of 579 outpatients with [major depressive disorder](#) with psychotic features. Efficacy was judged by several rating scales. Only 341 patients completed the trial. Both drug groups were significantly superior to placebo and there were no significant differences



between the two groups. Dothiepin was superior to [doxepin](#) relative to the incidence and severity of adverse events [794].

#### 4.6.O] Fluoxetine

##### 4.6.O.1] Depression

a) [Doxepin](#) and [fluoxetine](#) had similar efficacy in a comparative study involving 80 depressed patients (61 outpatients, 19 inpatients) diagnosed as having [major depressive disorder](#). The patients received either [fluoxetine](#) 20 to 60 milligrams/day (mean, 28.9 mg/day) or [doxepin](#) 100 to 200 milligrams/day (mean, 146.8 mg/day). Both treatment groups showed improvement over time, with no difference between [fluoxetine](#) and [doxepin](#) at study termination. The most common side effects of [fluoxetine](#) (headache, nausea, and insomnia) were in contrast to the pronounced anticholinergic side effects of [doxepin](#) (dry mouth, fatigue, constipation). Moreover, the significant weight gain associated with [doxepin](#) therapy was not seen with [fluoxetine](#) treatment [807].

b) [Fluoxetine](#) 20 to 80 milligrams daily (once daily or divided twice a day) and [doxepin](#) 50 to 200 milligrams daily (once daily or divided twice a day or three times a day) had comparable efficacy in the treatment of depression in geriatric patients (at least 64 years of age). Each drug was administered in increasing doses over the first two weeks of the study, with maintenance doses (up to 80 mg daily of [fluoxetine](#) and 200 mg daily of [doxepin](#)) being determined by the third week; this maintenance dose was given for three more weeks (total, six weeks). Both drugs were considered equally effective using the following parameters: Hamilton Psychiatric Rating Scale for Depression (HAM-D), Raskin Severity of Depression Scale, Covi Anxiety Scale, Clinical Global Impressions severity and improvement, Patient Global Improvement, and SCL-58 scales. Both drugs produced significant improvement compared to baseline scores. [Fluoxetine](#) was associated with a lower degree of drowsiness/sedation, dry mouth, constipation and vision disturbances. However, nervousness/anxiety, insomnia, sweating, [dyspepsia](#), and nausea occurred to a greater degree with [fluoxetine](#). Body weight decreased with [fluoxetine](#) and increased with [doxepin](#) [808].

c) In one study comparing [fluoxetine](#) and [doxepin](#), both drugs were effective in [major depressive disorder](#) in geriatric patients, with a lower incidence of side effects being observed with [fluoxetine](#) [808]. Weight loss occurred with [fluoxetine](#), as compared to weight gain with [doxepin](#), which was statistically significant. Heart rate was shown to increase in [doxepin](#)-treated patients as compared to decreases in [fluoxetine](#)-treated patients; this was also a statistically significant difference. Significant improvement in depressive symptoms was further demonstrated in a group (n=33) of geropsychiatric patients. Although this study only followed patients for a period of one month, significant side effects such as nausea, weight loss, and agitation were not noted. Doses of [fluoxetine](#) used were 20 mg every other day to 20 mg daily [809].

#### 4.6.P] Imipramine

##### 4.6.P.1] Depression

a) [Imipramine](#) may be slightly more effective than [doxepin](#) in the treatment of depression. Ninety-nine patients with [neurotic depression](#) received [imipramine](#) 100 to 200 milligrams/day or [doxepin](#) 100 to 200 milligrams/day for 4 weeks in a double-blind study. [Imipramine](#) was superior in 24 of 27 parameters. [Imipramine](#) was shown to be superior to [doxepin](#) in improving the symptoms of anxiety/depression; global evaluations showed improvement in 39 of 48 (81%) of [imipramine](#) patients and 34 and 49 (69%) of [doxepin](#) patients [801].

b) In a study involving 79 patients, a higher socioeconomic status and shorter duration of illness were indicative of a favorable response to [imipramine](#), whereas a higher response rate to [doxepin](#) was found in male patients [802].

c) [Amitriptyline](#) was superior to [imipramine](#) and [doxepin](#) in relation to their effects on interpersonal learning in 50 depressed inpatients [803]. All subjects performed better, according to quantitative indices

of learning tasks, than patients who received antipsychotic or neuroleptic drugs but no antidepressants. [Amitriptyline](#) patients scored significantly higher than either [imipramine](#) or [doxepin](#) patients.

d) No significant differences in overall efficacy of the 2 drugs was reported in one study [804], but [doxepin](#) 30 to 150 mg daily was superior to [imipramine](#) 150 mg daily in [neurotic depression](#), whereas [imipramine](#) appeared to be superior to [doxepin](#) in [endogenous depression](#) [805].

e) Similar antidepressant effects of [doxepin](#) and [imipramine](#) were reported; however, [imipramine](#) had a more rapid onset of action. [Doxepin](#) appeared to have more sustained effects [806].

#### 4.6.P.2) Efficacy

a) In elderly patients [doxepin](#) produces less orthostatic effects than [imipramine](#) (10.5 mmHg vs 25.9 mmHg). The orthostatic effect observed with [imipramine](#) was weakly related to dose and did not correlate with pretreatment orthostatic hypotension or with duration of treatment [800].

#### 4.6.Q) [Loxapine](#)

##### 4.6.Q.1) Anxiety

a) No significant differences were reported between [doxepin](#) and [loxapine](#) succinate in patients with [anxiety neurosis](#) [816].

#### 4.6.R) [Maprotiline](#)

##### 4.6.R.1) Depression

a) Single nightly doses of [doxepin](#) and [maprotiline](#), 75 to 150 milligrams orally for 6 weeks produced moderate to marked improvement in depression in a majority of 47 depressed patients. Both drugs were rated equally effective in this double-blind study. Side effects were not significantly different [814].

b) [Maprotiline](#) and [doxepin](#) were equally effective in a double-blind, multicenter trial in 95 depressed (neurotic and psychotic) inpatients/outpatients who were randomized into 2 equal groups [815]. A dose of 75 milligrams daily of either [maprotiline](#) or [doxepin](#) was given initially; the dose was doubled if needed. Seventy-eight patients completed the three-to-four week trial. The dropout group included six due to unwanted effects (2 [maprotiline](#), 4 [doxepin](#)), one from each group due to lack of efficacy and nine for other reasons (non-cooperation/noncompliance). Almost one-half of the patients in the study received additional psychoactive medication including sedatives, neuroleptics, and tranquilizers which were not thought to influence the trial. Overall assessment using a five point scale of target symptoms and a visual analogue scale showed no statistically significant difference between the two treatment groups. The most common side effects in both groups were dry mouth and fatigue. Fourteen patients continued treatment with [maprotiline](#) after the trial for a mean of 13 weeks (five received [maprotiline](#) for 30 weeks) with no pathological changes in laboratory values except for a slight rise in liver enzyme levels in two patients during initial therapy.

#### 4.6.S) [Mianserin](#)

##### 4.6.S.1) Mixed anxiety and [depressive disorder](#)

a) [Mianserin](#) 60 milligrams/day and [doxepin](#) 150 milligrams/day had similar efficacy in 60 patients with mixed anxiety/depression. After 4 weeks of treatment, there was no consistent difference in efficacy, but a higher incidence of side effects occurred in the [doxepin](#) group [810].

#### 4.6.T) [Nomifensine](#)

##### 4.6.T.1) Depression

a) [Doxepin](#) 186 mg daily was more effective than nomifensine 196 mg daily in treatment of endogenous and [neurotic depression](#) [799]. Fatigue and dizziness occurred more often with [doxepin](#) than nomifensine.

#### 4.6.U] [Opipramol](#)

##### 4.6.U.1] [Depression](#)

a) In a randomized double-blind 5-week trial, [doxepin](#) was found to be more effective overall than opipramol. Patients were diagnosed with one of the following types of depression: [neurotic depression](#), [psychotic depression](#), [involuntional melancholia](#) and senile depression. Eighteen patients were in the opipramol group and 22 in the [doxepin](#) group. The average dose of [doxepin](#) was between 10 and 20 milligrams (mg)/day and opipramol was between 50 and 100 mg/day. Effects of the drugs were viewed from three standpoints: nosologic classification, syndrome classification and individual symptoms. From the nosological standpoint, [doxepin](#) was significantly more effective; although opipramol was very effective in treating patients with [involuntional melancholia](#). From the syndrome classification standpoint, [doxepin](#) was once again better overall. From the individual symptoms standpoint, [doxepin](#) was more effective in relieving depressive mood, fear, suicidal thoughts, feeling of insufficiency, guilt, insomnia, vegetative symptoms and psychomotor disturbances than was opipramol. Drowsiness was the only adverse effect reported with either drug [813].

#### 4.6.V] [Paroxetine](#)

##### 4.6.V.1] [Depression](#)

a) [Paroxetine](#) was at least as effective as [doxepin](#) in the treatment of [major depression](#) in 272 geriatric patients in a double-blind, randomized trial. After a washout-period of 4 to 14 days, patients over 60 years of age received either [paroxetine](#) 10 to 40 milligrams (mg) (mean 23.4 mg) as a single daily dose or [doxepin](#) (up to 200 milligrams (mg), mean 105.2 mg/day) divided in two doses. Therapy continued for 42 days. [Paroxetine](#) was as effective as [doxepin](#) by several measures and more effective by others. [Doxepin](#) caused more sedation, confusion, and anticholinergic effects, and less nausea and headache compared with [paroxetine](#) [812].

#### 4.6.W] [Perphenazine/Amitriptyline Hydrochloride](#)

##### 4.6.W.1] [Depression](#)

a) [Doxepin](#) (100 to 150 milligrams/day) was not as effective as [amitriptyline/perphenazine](#) (100/8 to 150/12 milligrams/day) in 130 nonpsychotic depressed outpatients over 4 weeks. [Amitriptyline/perphenazine](#) produced greater improvement based on several rating scales. The combination also showed a greater incidence of anticholinergic and sedative side effects [811].

#### 4.6.X] [Trazodone](#)

##### 4.6.X.1] [Depression](#)

a) No significant difference in safety or efficacy was seen in a comparison of [trazodone](#) (mean daily dose during weeks 1, 3, and 6 was 125 milligrams (mg), 221 mg, and 246 mg) with [doxepin](#) (mean daily dose during weeks 1, 3, and 6 was 58 mg, 105 mg, and 127 mg) in 30 outpatients with [major depressive disorder](#) in a 6-week, double-blind, parallel study [823].

b) No significant difference was reported in a double-blind study of 101 patients, on the efficacy of [trazodone](#) and [doxepin](#) in the treatment of depression [824].

## 4.6.Y] Trimipramine

### 4.6.Y.1] Depression

a) The therapeutic efficacy and cardiac safety of trimipramine and doxepin were comparable in 37 patients with major depressive disorder. Patients received one week of placebo followed by five weeks of either trimipramine or doxepin in doses up to 200 milligrams/day. Based on ECG and psychiatric and cognitive function tests, the drugs were concluded to be equally safe and efficacious in this group of patients [825].

b) Trimipramine was superior to doxepin in safety and efficacy in a 4-week study. Trimipramine and doxepin (150 milligrams/day of each) were compared in 25 depressed hospitalized patients. Comparisons of efficacy favored trimipramine over doxepin. Doxepin had a higher incidence of side effects [826].

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