

DRUGDEX-EV 2426

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## CLOMIPRAMINE

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### 0.0] Overview

#### 1] Class

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

Antidepressant  
Central Nervous System Agent

#### 2] Dosing Information

a) [Clomipramine](#) Hydrochloride

##### 1] Adult

a) Delusional disorder

1) initial, 25 mg/day ORALLY, may increase dosage to 100 mg/day during the first 2 weeks (MAX dose 250 mg/day, mean dose 140 mg/day)

b) Depression

1) initial, 75 mg/day ORALLY (3 divided doses); may increase dosage slowly as needed and tolerated to a range of 100-250 mg/day (3 divided doses)

c) [Obsessive-compulsive disorder](#)

1) initial, 25 mg/day ORALLY, may increase dosage to 100 mg/day ORALLY during the first 2 weeks; MAX dose 250 mg/day [14]

d) [Panic disorder](#)

1) 25-75 mg/day ORALLY

**2) Pediatric**

- a) safety and effectiveness in children less than 10 years of age have not been established [14]

**1) Depression**

- a) 20-30 mg/day ORALLY; may increase dosage by 10 mg/day at 4-5 day intervals as needed and tolerated

**2) Obsessive-compulsive disorder**

- a) 10 years and older, initial, 25 mg/day ORALLY, may increase dosage to 3 mg/kg or 100 mg/day (whichever is less) ORALLY during the first 2 weeks; MAX dose 200 mg/day OR 3 mg/kg/day (whichever is less) [14]

**3) Contraindications****a) Clomipramine Hydrochloride**

- 1) coadministration with an MAOI, including linezolid and intravenous methylene blue, or within 14 days of MAOI discontinuation due to increased risk of serotonin syndrome [46]
- 2) hypersensitivity to clomipramine hydrochloride or other tricyclic antidepressants [46]
- 3) myocardial infarction; during the acute recovery period [46]

**4) Serious Adverse Effects****a) Clomipramine Hydrochloride**

- 1) Agranulocytosis
- 2) Cardiac arrest
- 3) Hepatotoxicity
- 4) Hyperglycemia
- 5) Increased body temperature
- 6) Leukopenia
- 7) Orthostatic hypotension
- 8) Pancytopenia
- 9) Prolonged QT interval
- 10) Seizure
- 11) Serotonin syndrome

12) Suicidal thoughts

13) Suicide

14) Syncope

15) [Thrombocytopenia](#)

5) Clinical Applications

a) [Clomipramine](#) Hydrochloride

1) FDA Approved Indications

a) [Obsessive-compulsive disorder](#)

2) Non-FDA Approved Indications

a) Delusional disorder

b) Depression

c) [Panic disorder](#)

1.0] Dosing Information

[Drug Properties](#)

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1.1] Drug Properties

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

B) Synonyms

Chlorimipramine

Chlorimipramine Hydrochloride

[Clomipramine](#)

[Clomipramine](#) HCl

[Clomipramine](#) Hydrochloride

C) Physicochemical Properties

1) Molecular Weight

a) [ClomiPRAMINE](#) hydrochloride: 351.3 [858]

2) pH

a) [ClomiPRAMINE](#) hydrochloride: pH of a 10% solution in water is 3.5 to 5 [859]

### 3) Solubility

a) **ClomiPRAMINE** hydrochloride: Freely soluble in water, in methanol, and in methylene chloride; insoluble in ethyl ether and in hexane [858]

## 1.2] Storage and Stability

### A) **Clomipramine** Hydrochloride

#### 1) Preparation

##### a) Oral route

##### 1) Administration

a) Divide total daily dose during titration phases and administer with meals to avoid gastrointestinal adverse effects [14].

## 1.3] Adult Dosage

### 1.3.1] Normal Dosage

#### 1.3.1.A] **Clomipramine** Hydrochloride

##### 1.3.1.A.1] Oral route

##### 1.3.1.A.1.a] **Obsessive-compulsive disorder**

1) The oral starting dose of **clomiPRAMINE** in the treatment of **obsessive-compulsive disorder** in adults is 25 mg daily, with gradual increase during the first 2 weeks, as tolerated, up to a daily maximum dose of 100 mg. Thereafter, the dosage may be gradually increased over the next several weeks, up to a daily maximum of 250 mg. While titrating to an individualized maintenance dose, divide the total daily dose and give with meals to reduce gastrointestinal side effects. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation [14].

##### 1.3.1.A.2] **Cataplexy - Narcolepsy**

See Drug Consult reference: **NARCOLEPSY AND CATAPLEXY - DRUG THERAPY**

### 1.3.4] Dosage in Geriatric Patients

#### A) **Clomipramine** Hydrochloride

1) Use caution in dosing **clomiPRAMINE** in geriatric patients; start at the lower end of the dosing range [14].

## 1.4] Pediatric Dosage

### 1.4.1] Normal Dosage

**1.4.1.A] Clomipramine Hydrochloride****1.4.1.A.1] Oral route****1.4.1.A.1.a] Obsessive-compulsive disorder**

1]) The oral starting dose of **clomiPRAMINE** in the treatment of **obsessive-compulsive disorder** in adolescents and children age 10 years and older is 25 mg daily, with gradual increase during the first 2 weeks, as tolerated, up to a daily maximum dose of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller. While titrating to an individualized maintenance dose, divide the total daily dose and give with meals to reduce gastrointestinal side effects. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation [14].

**1.4.1.A.1.b])** Safety and effectiveness in children less than 10 years of age have not been established [14].

**2.0] Pharmacokinetics****Onset and Duration****Drug Concentration Levels****ADME****2.1] Onset and Duration****A]) Onset****1]) Clomipramine Hydrochloride****a]) Initial Response**

1]) Obsessive-compulsive disorder, oral: 4 to 10 weeks [563].

2]) Obsessive-compulsive disorder, intravenous: 5.5 days [564].

3]) Depression, oral: 2 weeks [565].

**2.2] Drug Concentration Levels****A]) Clomipramine Hydrochloride****1]) Therapeutic Drug Concentration**

a]) **Obsessive-compulsive disorder**, 100 to 250 ng/mL (**clomiPRAMINE**) plus 230 to 550 ng/mL (desmethylclomipramine) [568] [569].

b]) Depression, greater than 160 to 200 ng/mL **clomiPRAMINE** plus desmethylclomipramine [570].

1]) In a dose-effect study, there was a pronounced inter-patient variability in response. The authors attributed this to a variability in **clomiPRAMINE** steady state kinetics,

clomiPRAMINE dose-dependent kinetics, and genetic polymorphism related to CYP2D6 [571].

**2)) Time to Peak Concentration**

**a))** Oral: 2 to 6 hours (mean, 4.7 hours) [567] [566].

**3)) Area Under the Curve**

**a))** 600 ng/ml (0.7 mg/kg) [566].

**2.3] ADME**

**2.3.1] Absorption**

**A)) Clomipramine** Hydrochloride

**1)) Bioavailability**

**a))** Oral: 20% to 78% [572] [573]

**2)) Effects of Food**

**a))** None [567].

**2.3.2] Distribution**

**A)) Distribution Sites**

**1)) Clomipramine** Hydrochloride

**a)) Protein Binding**

**1))** 97% [567] [576].

**a))** Principally bound to albumin [567].

**b)) OTHER DISTRIBUTION SITES**

**1))** Cerebrospinal fluid (CSF), CSF:plasma ratio is 2.6 [567].

**B)) Distribution Kinetics**

**1)) Clomipramine** Hydrochloride

**a)) Volume of Distribution**

**1))** 12 L/kg (range, 7 to 20 L/kg) [577].

### 2.3.3] Metabolism

#### A) Metabolism Sites and Kinetics

##### 1) Clomipramine Hydrochloride

###### a) Liver [577].

1) Extensive first-pass effect [577].

2) The metabolism of clomiPRAMINE and desmethyldomipramine may be capacity limited [567].

#### B) Metabolites

##### 1) Clomipramine Hydrochloride

###### a) Desmethyldomipramine, active [577].

1) Responders had a trend towards lower plasma desmethyldomipramine to clomiPRAMINE ratios [578].

###### b) 8-OH clomiPRAMINE and 8-OH desmethyldomipramine [568].

### 2.3.4] Excretion

#### A) Kidney

##### 1) Clomipramine Hydrochloride

###### a) Renal Excretion (%)

1) 51% to 60% recovered in the urine [567].

#### B) Feces

##### 1) Clomipramine Hydrochloride

###### a) 24% to 32% recovered in the feces [567].

#### C) Total Body Clearance

##### 1) Clomipramine Hydrochloride

###### a) 12.7 to 56.5 L/hr [579].

1) In an interethnic study comparing the clearance of clomiPRAMINE between Japanese and Swedish patients, Japanese patients had a much lower clearance (12.7 L/hr) than the Swedish patients (62.7 L/hr) [579].

### 2.3.5] Elimination Half-life

#### A) Parent Compound

##### 1) [Clomipramine](#) Hydrochloride

a) 19 to 37 hours (mean, 32 hours) [567] [580].

1) The half-life of clomiPRAMINE may be lengthened at higher doses (200 to 250 mg/day) [567].

#### B) Metabolites

##### 1) [Clomipramine](#) Hydrochloride

a) Desmethyldomipramine, 54 to 77 hours (mean, 69 hours) [567].

### 3.0] Cautions

[Contraindications](#)

[Precautions](#)

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#### 3.0.A] Black Box WARNING

#### Clomipramine Hydrochloride

##### Oral (Capsule)

Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24, and there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Monitor patients closely for clinical worsening, suicidality, or unusual changes in behavior. These risks must be balanced with clinical need. Families and caregivers should closely observe the patient and stay in close contact with the prescriber. This drug is not approved for use in pediatric patients except for those with obsessive compulsive disorder (OCD) [46].

### 3.1] Contraindications

#### A) [Clomipramine](#) Hydrochloride

1) coadministration with an MAOI, including [linezolid](#) and intravenous methylene blue, or within 14 days of MAOI discontinuation due to increased risk of [serotonin syndrome](#) [46]

2) hypersensitivity to [clomiPRAMINE](#) hydrochloride or other tricyclic antidepressants [46]



3)) [myocardial infarction](#); during the acute recovery period [46]

### 3.2] Precautions

#### A)) [Clomipramine](#) Hydrochloride

1)) Black Box Warning:

2)) -- increased risk of suicidality or worsening depression, especially in children, adolescents, and young adults during the first few months or therapy or dose adjustments; monitoring recommended; discontinuation may be required [46]

3)) -- avoid use in pediatric patients without diagnosed [obsessive-compulsive disorder](#) [46]

4)) Cardiovascular:

5)) -- patients with [cardiovascular disease](#) at increased risk for hypotension, [tachycardia](#), or ECG changes; [46]

6)) -- increased risk of hypertensive crises in patients with [adrenal neoplasm](#) (eg, [pheochromocytoma](#), [neuroblastoma](#)) [46]

7)) -- [cardiac toxicity](#) may occur in patients with [hyperthyroidism](#) or with concurrent use of thyroid drugs [46]

8)) Endocrine Metabolic Effects:

9)) -- [hyperthermia](#) has been reported during post marketing surveillance [46]

10)) -- significant weight gain may occur [46]

11)) Hematologic:

12)) -- hematologic toxicities, including [pancytopenia](#), [anemia](#), [thrombocytopenia](#), [agranulocytosis](#) and [leukopenia](#) have been reported [46]

13)) Hepatic Effects:

14)) -- severe or fatal [hepatic injury](#) has rarely been reported; monitoring recommended in patients with history of [hepatic impairment](#) [46]

15)) Neurologic:

16)) -- seizures, with rare fatalities, have been reported, with greater risk with drugs or conditions that may lower the seizure threshold (eg, seizure history, alcoholism, brain damage) [46]

17)) -- [neuroleptic malignant syndrome](#) has been reported [46]

18)) Ophthalmic Effects:

19)) -- use caution in patients with elevated intraocular pressure or history of [narrow-angle glaucoma](#) due to potential anticholinergic effects [46]

20)) -- [angle-closure glaucoma](#) may occur in patients with anatomically narrow angles and without a patent [iridectomy](#) [46]

**21)) Psychiatric Effects:**

**22))** -- antidepressants may trigger a mixed/[manic episode](#) in patients with underlying [bipolar disorder](#); baseline screening recommended [46]

**23))** -- [psychosis](#) may occur in patients with undetected [schizophrenia](#) [46]

**24))** -- neuropsychiatric signs and symptoms (ie, paranoia, confusion, psychotic episodes, hallucinations, delusions) have been reported [46]

**25))** -- [hypomania](#) or mania have been reported in patients with affective disorder [46]

**26)) Renal Effects:**

**27))** -- use caution in patients with a history of urinary retention due to potential anticholinergic effects [46]

**28))** -- use caution in patients with significant [renal impairment](#) [46]

**29)) Reproductive Effects:**

**30))** -- increased incidence of male sexual dysfunction (eg, ejaculatory failure, impotence) has been reported [46]

**31)) Other:**

**32))** -- concurrent use with [electroconvulsive therapy](#) (ECT) may increase ECT hazards [46]

**33))** -- discontinuation recommended before elective surgery with general anesthetics [46]

**34))** -- serious withdrawal symptoms have occurred with abrupt discontinuation; tapering recommended with careful monitoring [46]

**35)) Concomitant Use:**

**36))** -- concomitant use with serotonergic drugs (ie, triptans, tricyclic antidepressants, [fentanyl](#), [lithium](#), [tramadol](#), tryptophan, [buspirone](#), St John's wort) increases risk of [serotonin syndrome](#); monitoring recommended; discontinue use if suspected [46]

**3.3] Adverse Reactions****3.3.1] Cardiovascular Effects****3.3.1.A] Clomipramine Hydrochloride****3.3.1.A.1] Cardiac arrest**

**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) [55].

**b)** In a case report, a 31-year-old severely depressed woman developed severe [epileptic convulsions](#) followed by [cardiac ARREST](#) during a 300 mg infusion of parenteral [clomiPRAMINE](#) [56]. The patient had been started on parenteral [clomiPRAMINE](#) 25 mg/day which was slowly increased to 250 mg/day over 14 days. The [cardiac arrest](#) occurred on day 15 of treatment. She was resuscitated by external [cardiac massage](#); EKG showed slight T wave flattening. One week later the patient restarted on oral [clomiPRAMINE](#) and was discharged 6 weeks later with no further cardiac problems.

### 3.3.1.A.2] Orthostatic hypotension

**a)** Incidence: 4% to 6% [14]

**b)** Adults

**1)** In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of postural hypotension was 6% with [clomiPRAMINE](#) (n=322) compared with 0% with placebo (n=319) [14].

**2)** Orthostatic hypotension worsened in both younger (less than 55 years of age, n=74) and older (55 to 70 years of age, n=28) people after taking [clomiPRAMINE](#) 150 milligrams per day for 2 weeks, but the fall in blood pressure was more severe in the older population [57].

**3)** A 57-year-old man who had been taking [clomiPRAMINE](#) 150 milligrams at bedtime for 2 years developed hypotension when he received general [anesthesia](#) in preparation for mitral valve repair. [Anesthesia](#) was induced with sodium [thiopental](#) and [fentanyl](#) and maintained with [isoflurane](#). Forty-five minutes after [induction of anesthesia](#), blood pressure and vascular resistance declined. Blood pressure was unresponsive to [ephedrine](#), [phenylephrine](#), and [dopamine](#). After skin incision and [sternotomy](#), systolic blood pressure decreased precipitously, to 55 millimeters of mercury. Despite multiple boluses of [ephedrine](#) and an infusion of [norepinephrine](#), the patient developed [third-degree atrioventricular block](#). [Cardiopulmonary bypass](#) was begun, and the surgery proceeded. The dosage of [norepinephrine](#) was increased before weaning from [cardiopulmonary bypass](#). Prior to surgery, the patient had experienced postural hypotension, which was attributed to [clomiPRAMINE](#). Therefore, a presumptive diagnosis of [clomiPRAMINE](#)-induced hypotension precipitated by [anesthesia](#) was made, and [clomiPRAMINE](#) was withheld. The patient was gradually weaned from [norepinephrine](#) [58].

**c)** Pediatrics

**1)** In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of postural hypotension was 4% with [clomiPRAMINE](#) (n=46) compared with 0% with placebo (n=44) [14].

### 3.3.1.A.3] Palpitations

**a)** Incidence: 4% [14]

**b)** Adults

1j) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of palpitations was 4% with [clomiPRAMINE](#) (n=322) compared with 2% with placebo (n=319) [14].

c) Pediatrics

1j) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of palpitations was 4% with [clomiPRAMINE](#) (n=46) compared with 0% with placebo (n=44) [14].

### 3.3.1.A.4] Prolonged QT interval

a) In a prospective population-based cohort study (n=8222; Rotterdam Study), patients taking tricyclic antidepressant drugs had a significant increase in corrected QT (QTc) interval compared with non-users. All participants were 55 years or older (mean age, 66.7 +/- 8.6 years) at first ECG; women were significantly older and more prevalent throughout the study. Each individual had 1 to 4 ECGs analyzed and were followed for up to 14 years. The threshold for prolonged QTc, as defined by European regulatory guidelines for QTc intervals, was 450 and 470 milliseconds (msec) in men and women, respectively. Gender differences existed for mean baseline QTc (422.4 vs 432.1 msec in men and women, respectively); although, each was within the defined gender-specific normal range for QTc. Cross-sectional and within-person longitudinal analysis of QTc were performed on 17,516 ECGs, and the overall effect of different psychotropic classes on QTc was estimated. In the cross-sectional analysis, patients taking tricyclic antidepressants (n=177) had prolonged QTc intervals compared with non-users, with a mean increase of 6.9 msec (95% CI, 3.1 to 10.7; p less than 0.05). Longitudinal analysis showed patients starting a tricyclic antidepressant (n=66) had prolonged QTc intervals in 2 subsequent ECGs compared with non-users, with a mean increase of 10.4 msec (95% CI, 3.5 to 17.4; p less than 0.05). Tricyclic antidepressants studied were [amitriptyline](#), [clomiPRAMINE](#), [doxepin](#), [imipramine](#), [maprotiline](#), and [nortriptyline](#) [59].

b) In a study of psychiatric patients, use of tricyclic antidepressants was associated with an increased risk of prolonged corrected QT (QTc) interval (adjusted odds ratio, 4.4; 95% CI, 1.6 to 12.1; p=0.004) compared with healthy volunteers. Patients receiving mental health care at facilities of varied acuity (n=495; 198 females; mean age, 45 years; range, 18 to 74 years), were evaluated for prolonged QTc interval. Patients with pre-existing [cardiovascular disease](#) (n=71) were included in the study; although, patients with [atrial fibrillation](#) and [bundle-branch block](#) were excluded. The ECGs from healthy volunteers (n=101; 60 females; mean age, 35 years; range, 20 to 53 years) served as a reference to establish an abnormally lengthened QTc interval. The threshold for QTc lengthening, defined as 2 SD above the mean value from the reference group, was QTc greater than 456 milliseconds. More than 30 different psychotropics were prescribed amongst the patients, and many patients were on more than one drug. Lengthened QTc occurred in 40 (8%) of all 495 patients, including 5 patients taking tricyclic monotherapy (n=44; 11%). Of all patients exposed to tricyclic antidepressant therapy (n=97), QTc lengthening occurred in 13 cases. No analysis was performed for individual tricyclic antidepressant drugs, and serum potassium was not measured during this study [60].

c) Children and adolescents treated with [clomiPRAMINE](#) hydrochloride and [desipramine](#) hydrochloride for [obsessive compulsive disorder](#) (OCD) had an increased risk of prolonged corrected QT (QTc) interval at short-term and long-term follow up. The ECGs of children and adolescents (n=47; 33 males; mean age, 13.5 +/- 2.8 years; range, 7 to 17 years) enrolled in [clomiPRAMINE](#) trials were examined at baseline, after 5 weeks, and periodically during long-term treatment. Baseline ECGs were taken after a 1 month drug-free interval and prolonged QTc was defined as greater than or equal to 440 milliseconds (msec). All patients had received 5 weeks of [clomiPRAMINE](#) treatment at the week 5 ECG evaluation; 8 as part of a [clomiPRAMINE](#)/placebo crossover study,

and 39 as part of a [clomiPRAMINE/desipramine](#) crossover study (5 weeks of each drug). After short-term treatment, 25 patients continued on [clomiPRAMINE](#) maintenance therapy (mean, 24.6 +/- 7.6 months). All dosages were targeted to 3 mg/kg/day; the mean short-term [clomiPRAMINE](#) and [desipramine](#) dosages were 150 +/- 54 mg/day and 157 +/- 50 mg/day, respectively, and the mean long-term [clomiPRAMINE](#) dosage was 150 +/- 59 mg/day. Analysis of week 5 ECGs (n=39) demonstrated significantly increased mean QTc intervals compared with baseline for both [clomiPRAMINE](#) (422.3 +/- 17.48 msec vs 397.97 +/- 18.94 msec; p less than 0.05) and [desipramine](#) (414.79 +/- 15.77 msec vs 397.97 +/- 18.94 msec; p less than 0.05), and a between drug difference as [clomiPRAMINE](#) increased QTc interval more than [desipramine](#) (p less than 0.05). Prolonged QTc occurred in 5% (n=2/39) and 11% (n=5/47) of patients during short-term treatment with [desipramine](#) and [clomiPRAMINE](#), respectively. Significant increase of QTc interval was also seen during long-term use of [clomiPRAMINE](#) compared with baseline (mean, 424 +/- 27.1 msec vs 398.44 +/- 22.2 msec; p less than 0.05). Prolonged QTc occurred in 20% (n=5/25) of patients during long-term [clomiPRAMINE](#) use, 1 case existed at baseline. Neither drug dosages nor plasma drug concentrations correlated with change of QTc interval for either drug studied [61].

### 3.3.1.A.5] Syncope

a) Incidence: 2% [14]

b) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of syncope was 2% with [clomiPRAMINE](#) (n=46) compared with 0% with placebo (n=44) [14].

### 3.3.1.A.6] Tachycardia

a) Incidence: 2% to 4% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of [tachycardia](#) was 4% with [clomiPRAMINE](#) (n=322) compared with 0% with placebo (n=319) [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of [tachycardia](#) was 2% with [clomiPRAMINE](#) (n=46) compared with 0% with placebo (n=44) [14].

## 3.3.2] Dermatologic Effects

### 3.3.2.A] Clomipramine Hydrochloride

#### 3.3.2.A.1] Diaphoresis

a) Incidence: 9% to 29% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of increased sweating was 29% with [clomiPRAMINE](#) treatment (n=322) compared with 3% with placebo (n=319) [14].

2) Increased sweating was experienced by significantly more patients on [clomiPRAMINE](#) 50 to 300 mg/day than those on placebo during clinical trials of agoraphobic and obsessive compulsive patients [84] [72].

**c) Pediatrics**

1) In placebo-controlled clinical trials of children and adolescents with **obsessive compulsive disorder** (OCD), the incidence of increased sweating was 9% with **clomiPRAMINE** treatment (n=46) compared with 0% with placebo (n=44) [14].

**3.3.2.A.2] Discoloration of skin**

a) A case of pseudocyanotic pigmentation has occurred with **clomiPRAMINE** [85].

**3.3.2.A.3] Flushing**

a) Incidence: 7% to 8% [14]

**b) Adults**

1) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of flushing was 8% with **clomiPRAMINE** treatment (n=322) compared with 0% with placebo (n=319) [14].

**c) Pediatrics**

1) In placebo-controlled clinical trials of children and adolescents with **obsessive compulsive disorder** (OCD), the incidence of flushing was 7% with **clomiPRAMINE** treatment (n=46) compared with 0% with placebo (n=44) [14].

**3.3.2.A.4] Flushing, Unrelated to menopause**

a) Incidence: 2% to 5% [14]

**b) Adults**

1) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of hot flushes not related to menopause was 5% with **clomiPRAMINE** treatment (n=322) compared with 0% with placebo (n=319) [14].

**c) Pediatrics**

1) In placebo-controlled clinical trials of children and adolescents with **obsessive compulsive disorder** (OCD), the incidence of hot flushes was 2% with **clomiPRAMINE** treatment (n=46) compared with 0% with placebo (n=44) [14].

**3.3.2.A.5] Pruritus**

a) Incidence: 6% [14]

b) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of **pruritus** was 6% with **clomiPRAMINE** treatment (n=322) compared with 0% with placebo (n=319) [14].

**3.3.2.A.6] Rash**

a) Incidence: 8% [14]

b) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of skin rash with **clomiPRAMINE** treatment (n=322) was 8% compared to 1% with placebo (n=319) [14].

**3.3.3] Endocrine/Metabolic Effects**



### 3.3.3.A] Clomipramine Hydrochloride

#### 3.3.3.A.1] Galactorrhea

a) Incidence: 4% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of nonpuerperal lactation was 4% with [clomiPRAMINE](#) treatment (females; n=182) compared with 0% with placebo (females; n=167) [14].

c) Several cases of [hyperprolactinemia](#) and [galactorrhea](#) have been reported with [clomiPRAMINE](#) therapy. A severely depressed woman in her late twenties was admitted to a psychiatric unit and started on oral [clomiPRAMINE](#) 75 mg twice daily and L-tryptophan 1 g 3 times daily. Two days later the patient developed profuse [galactorrhea](#) which was associated with [amenorrhea](#). L-tryptophan was reduced and eventually stopped over a 3-week period with no change in breast secretion. [ClomiPRAMINE](#) was reduced to 25 mg twice daily and [bromocriptine](#) 2.5 mg twice daily was initiated. [Galactorrhea](#) gradually resolved after 6 weeks of this therapy and menstruation also returned at this time [77].

d) A woman who had been on oral [clomiPRAMINE](#) 10 mg twice daily for several years for anxiety developed [galactorrhea](#), loss of libido, and uncomfortable breast engorgement 6 months after an increase of [clomiPRAMINE](#) to 50 mg at night [78]. Her plasma prolactin levels were also above normal. [ClomiPRAMINE](#) was discontinued and within 2 weeks [galactorrhea](#) was reduced; within 3 months her breasts became normal and [galactorrhea](#) had resolved.

#### 3.3.3.A.2] Hyperglycemia

a) [Hyperglycemia](#), glucosuria and [diabetes mellitus](#) has been reported with the use of [clomiPRAMINE](#) [14].

b) An 84-year-old woman developed severe [hyperglycemia](#) within 5 months following the initiation of [clomiPRAMINE](#) 25 mg/day. The patient had a medical history of well-controlled [hypertension](#), [atrial fibrillation](#) and concomitant medications included [aspirin](#) and [irbesartan](#). Her BMI was 23 kg/m(2) and she had a negative family history of [diabetes](#) or [glucose intolerance](#). Upon physical examination the patient was dehydrated and neurological examination noted obtunded consciousness without other abnormalities. Laboratory analysis revealed severe [hyperglycemia](#) (serum glucose, 459 mg/dL (25.5 mmol/L)), [ketonemia](#), [metabolic acidosis](#), elevated [HbA1C](#) level (12%), serum sodium (158 mmol/L), SCr (1.8 mg/dL), glycosuria and ketonuria. Additional laboratory test results were within normal ranges (eg, CBC, serum lipase and [serum amylase](#)) and chest radiography and CT of the head and abdomen were unremarkable. Upon hospitalization, the [clomiPRAMINE](#) was discontinued and the patient was treated with IV [insulin](#) (30 units/day) and IV fluids. The patient's blood glucose level normalized with treatment and after 10 days, the [insulin](#) therapy was discontinued and the patient was discharged from the hospital. Three months after hospital discharge, laboratory analysis reported [HbA1C](#) level at 5% and the patient agreed to restart the [clomiPRAMINE](#) under medical surveillance. One week after restarting the [clomiPRAMINE](#), the patient developed [hyperglycemia](#) (serum glucose, 250 mg/dL (13.88 mmol/L)), glycosuria, and ketonuria. Again, the [clomiPRAMINE](#) was discontinued and the blood glucose normalized after 2 days. A temporal relationship appears to exist between the administration of [clomiPRAMINE](#) and the development of [hyperglycemia](#) and with the resolution of the [hyperglycemia](#) upon withdrawal of [clomiPRAMINE](#) [81].

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

a) More than 30 cases of [hyperthermia](#) have been associated with [clomiPRAMINE](#). Most instances occurred when [clomiPRAMINE](#) was used in combination with other drugs. [Neuroleptic malignant](#)

[syndrome](#) has developed when [clomiPRAMINE](#) was administered concomitantly with a neuroleptic agent [53].

**b)** Sixteen of 38 inpatients with DSM-III-R [major depression](#) treated with [clomiPRAMINE](#) alone developed at least one symptom of the [serotonin syndrome](#) in a prospective study [69]. This syndrome includes confusion, agitation, myoclonus, diaphoresis, tremor, and diarrhea. In 14 cases, tremor and myoclonus occurred simultaneously and 10 patients presented tremor, myoclonus, diaphoresis, and shivering. With the exception of 2 patients, symptoms were transient, lasted less than 1 week, and resolved with treatment.

**c)** Two cases of clomiPRAMINE-moclobemide overdose resulted in fatal [serotonin syndrome](#) [80]. A 23-year-old male and 19-year-old female ingested 1000-1500 mg moclobemide, an MAO-A selective inhibitor and 225 to 500 mg [clomiPRAMINE](#) in order to "get high". Two to 3 hours later they were euphoric, but developed extreme tremor within the next 2 hours followed by convulsions and loss of consciousness. Both patients died 9 to 10 hours after ingestion, one in [status epilepticus](#) and the other while in [hyperthermia](#) following generalized epileptiform convulsions. Blood levels of both drugs at autopsy were lower than expected, based on the estimated amount of drug ingested. This may reflect prolonged absorption or postmortem redistribution. There were no levels of desmethyl or hydroxy metabolites of [clomiPRAMINE](#) reported.

#### 3.3.3.A.4] Syndrome of [inappropriate antidiuretic hormone secretion](#)

**a)** [Hyponatremia](#) secondary to the syndrome of [inappropriate antidiuretic hormone secretion](#) (SIADH) has been attributed to [clomiPRAMINE](#) [79]. [Hyponatremia](#) developed in a 64-year-old woman 2 days following initiation of [clomiPRAMINE](#) 25 g three times daily. The patient was not receiving other medications. [ClomiPRAMINE](#) was discontinued and electrolyte levels a week later were normal.

#### 3.3.3.A.5] Weight decreased

**a)** Incidence: 5% to 7% [14]

**b)** The incidence of weight loss, at least 7% of initial body weight, was 5% in controlled studies of adults receiving [clomiPRAMINE](#) (n=322) compared with 1% of patients administered placebo (n=319) [14].

**c)** In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of weight loss with [clomiPRAMINE](#) treatment (n=46) was 7% compared to 0% with placebo (n=44) [14].

#### 3.3.3.A.6] Weight increased

**a)** Incidence: 18% [14]

**b)** The incidence of weight gain was 18% in controlled studies of adults receiving [clomiPRAMINE](#) (n=322) compared with 1% of patients receiving placebo (n=319). Twenty-eight percent of these patients had weight gain of at least 7% of their initial body weight and several patients had weight gain in excess of 25% of their initial body weight [14].

### 3.3.4] Gastrointestinal Effects

#### 3.3.4.A] [Clomipramine Hydrochloride](#)

##### 3.3.4.A.1] Constipation

**a)** Incidence: 22% to 47% [14]

**b)** Adults



1j) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of constipation was 47% with [clomiPRAMINE](#) treatment (n=322) compared with 11% with placebo (n=319) [14].

c) Pediatrics

1j) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of constipation was 22% with [clomiPRAMINE](#) treatment (n=46) compared with 9% with placebo (n=44) [14].

**3.3.4.A.2] Diarrhea**

a) Incidence: 13% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of diarrhea was 13% with [clomiPRAMINE](#) treatment (n=322) compared with 9% with placebo (n=319) [14].

**3.3.4.A.3] Flatulence**

a) Incidence: 6% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of flatulence was 6% with [clomiPRAMINE](#) treatment (n=322) compared with 3% with placebo (n=319) [14].

**3.3.4.A.4] Increased appetite**

a) Incidence: 11% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of increased appetite was 11% with [clomiPRAMINE](#) treatment (n=322) compared with 2% with placebo (n=319) [14].

**3.3.4.A.5] Indigestion**

a) Incidence: 13% to 22% [14]

b) Adults

1j) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of [dyspepsia](#) was 22% with [clomiPRAMINE](#) treatment (n=322) compared with 10% with placebo (n=319) [14].

c) Pediatrics

1j) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of [dyspepsia](#) was 13% with [clomiPRAMINE](#) treatment (n=46) compared with 2% with placebo (n=44) [14].

**3.3.4.A.6] Loss of appetite**

a) Incidence: 12% to 22% [14]

b) Adults

1j) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of anorexia was 12% with [clomiPRAMINE](#) treatment (n=322) compared with 0% with placebo (n=319) [14].

**c) Pediatrics**

**1)** In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of anorexia was 22% with [clomiPRAMINE](#) treatment (n=46) compared with 2% with placebo (n=44) [14].

**3.3.4.A.7] Nausea**

**a)** Incidence: 33% [14]

**b)** In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of nausea was 33% with [clomiPRAMINE](#) treatment (n=322) compared with 14% with placebo (n=319) [14].

**3.3.4.A.8] Taste sense altered**

**a)** Incidence: 4% to 8% [14]

**b) Adults**

**1)** In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of taste perversion was 8% with [clomiPRAMINE](#) treatment (n=322) compared with 0% with placebo (n=319) [14].

**c) Pediatrics**

**1)** In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of taste perversion was 4% with [clomiPRAMINE](#) treatment (n=46) compared with 0% with placebo (n=44) [14].

**3.3.4.A.9] [Tooth disorder](#)**

**a)** Incidence: 5% [14]

**b)** In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of [tooth disorder](#) was 5% with [clomiPRAMINE](#) treatment (n=322) compared with 0% with placebo (n=319) [14]. The [tooth disorder](#) was not characterized further.

**3.3.4.A.10] Vomiting**

**a)** Incidence: 7% [14]

**b) Adults**

**1)** In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of vomiting was 7% with [clomiPRAMINE](#) treatment (n=322) compared with 2% with placebo (n=319) [14].

**c) Pediatrics**

**1)** In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of vomiting was 7% with [clomiPRAMINE](#) treatment (n=46) compared with 0% with placebo (n=44) [14].

**3.3.4.A.11] [Xerostomia](#)**

**a)** Incidence: 63% to 84% [14]

**b) Adults**

1j) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of dry mouth was 84% with [clomiPRAMINE](#) treatment (n=322) compared with 17% with placebo (n=319) [14].

c) Pediatrics

1j) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of dry mouth was 63% with [clomiPRAMINE](#) treatment (n=46) compared with 16% with placebo (n=44) [14].

### 3.3.5] Hematologic Effects

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

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

a) [Agranulocytosis](#) has been reported with tricyclic antidepressants [47] [48] [49] and [clomiPRAMINE](#) has been associated with this syndrome. A 37-year-old depressed woman received a total of 2.65 grams of both oral and parenteral [clomiPRAMINE](#) over a 26-day period [50]. She developed a sore throat and fever 3 weeks after stopping treatment. A white cell count revealed a complete absence of neutrophils. The patient developed a [candida infection](#) and was admitted to the hospital for antibiotic therapy. After 12 days of [neutropenia](#), there was an increase in the [lymphocyte](#) count followed by a sudden reappearance of neutrophils. Clinical improvement was noted with the reappearance of neutrophils and the patient was discharged 40 days after admission. In a second report, a 49-year-old postmenopausal Caucasian female was treated with [clomiPRAMINE](#) 150 mg at bedtime for 38 days. Four days after stopping the drug, a routine [hemogram](#) revealed [leukopenia](#): 1200/mm(3) from 4500/mm(3) one month earlier. One week later, the white blood cell count was 4200 and the [agranulocytosis](#) had resolved [51].

b) A 67-year-old man developed concurrent severe [agranulocytosis](#) with elevation of hepatic transaminases after treatment with [clomiPRAMINE](#) (CMI) for 1 month at 175 mg/day. The white count returned to normal 14 days after discontinuation of CMI [52].

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

a) [ClomiPRAMINE](#) has caused [leukopenia](#), among other [hematologic disorders](#). [Leukocyte](#) and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with [clomiPRAMINE](#) [53].

##### 3.3.5.A.3] [Pancytopenia](#)

a) [ClomiPRAMINE](#) has caused [pancytopenia](#), among other [hematologic disorders](#). [Leukocyte](#) and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with [clomiPRAMINE](#) [53].

b) A 54-year-old man developed [pancytopenia](#) after being treated with oral [clomiPRAMINE](#) 50 mg/day for approximately 40 days and parenteral [clomiPRAMINE](#) 50 mg/day for several days before the onset of symptoms [54]. Several days after admission the patient experienced increased fatigue, drowsiness, pallor and ecchymoses on the arms. A [complete blood count](#) revealed a progressive reduction of all cell lines, with [platelets](#) and white blood cells leading the way. On day 20 after admission [clomiPRAMINE](#) was discontinued and his blood count began to rise. The patient was discharged on day 49 with his blood count still below baseline, but continuing to rise.

##### 3.3.5.A.4] [Thrombocytopenia](#)

a) ClomiPRAMINE has caused thrombocytopenia, among other hematologic disorders. Leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with clomiPRAMINE [53].

### 3.3.6] Hepatic Effects

#### 3.3.6.A] Clomipramine Hydrochloride

##### 3.3.6.A.1] Allergic hepatitis

a) A 41-year-old woman developed allergic hepatitis with extreme eosinophilia during the second month of treatment with clomiPRAMINE for suicidal depression. After 4 weeks of clomiPRAMINE treatment (dose increments to 150 milligrams/day), she developed right-sided upper abdominal pain and had fever, which normalized after 2 days. Abdominal pain persisted. Liver enzymes were elevated, but there was no eosinophilia. By 6 weeks, eosinophils had increased to 65% of the differential white blood cell count. Allergic hepatitis was diagnosed and clomiPRAMINE was discontinued. Hematopoietic side-effects disappeared within 2 weeks. Liver function took longer to normalize. Her depression was then successfully treated with a chemically unrelated substance (moclobemide) [83].

##### 3.3.6.A.2] Hepatotoxicity

a) Incidence: 1% to 3%

b) ClomiPRAMINE has induced elevated aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) in approximately 1% and 3% of patients, respectively, to levels 3 times the upper limit of normal [53]. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzymes is recommended in such patients.

c) A 67-year-old man developed concurrent severe agranulocytosis with elevation of hepatic transaminases after treatment with clomiPRAMINE (CMI) for 1 month at 175 mg/day. The white count returned to normal 14 days after discontinuation of CMI [52].

### 3.3.8] Musculoskeletal Effects

#### 3.3.8.A] Clomipramine Hydrochloride

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

a) In a case-control study including fracture cases (n=124,655) during the year 2000 and age- and gender-matched controls (n=373,962), there was an increased risk of any fracture in participants who were using an average standard daily dose of clomiPRAMINE (adjusted odds ratio (OR), 1.49; 95% CI, 1.19 to 1.88) compared to those who were not exposed to clomiPRAMINE. ClomiPRAMINE use was associated with an increased risk of hip fracture (adjusted OR, 2.04; 95% CI, 1.11 to 3.75), but not forearm (adjusted OR, 1.61; 95% CI, 0.89 to 2.89) or spine fracture (adjusted OR, 2.79; CI, 0.88 to 8.8) [86]

b) 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 [87].

#### **3.3.8.A.2] Increased muscle tone**

a) Incidence: 4% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of hypertonia was 4% with [clomiPRAMINE](#) treatment (n=322) compared with 1% with placebo (n=319) [14].

#### **3.3.8.A.3] Myalgia**

a) Incidence: 13% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of myalgia was 13% with [clomiPRAMINE](#) treatment (n=322) compared with 9% with placebo (n=319) [14].

### **3.3.9] Neurologic Effects**

#### **3.3.9.A] Clomipramine Hydrochloride**

##### **3.3.9.A.1] Disturbance in thinking**

a) Incidence: 1% or greater [14]

b) During premarketing clinical testing of [clomiPRAMINE](#) in the United States, abnormal thinking was reported on 1 or more occasions in at least 1% of patients (n=3525) [14].

##### **3.3.9.A.2] Dizziness**

a) Incidence: 41% to 54% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of dizziness was 54% with [clomiPRAMINE](#) (n=322) compared with 14% with placebo (n=319) [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of dizziness was 41% with [clomiPRAMINE](#) (n=46) compared with 14% with placebo (n=44) [14].

##### **3.3.9.A.3] Feeling nervous**

a) Incidence: 2% to 18% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of nervousness with [clomiPRAMINE](#) treatment (n=322) was 18% compared to 2% with placebo (n=319) [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of nervousness was 4% with [clomiPRAMINE](#) (n=46) compared with 2% with placebo (n=44) [14].

### 3.3.9.A.4] Gilles de la Tourette's syndrome

a) Vocal and motor tics (Tourettism) developed after administration of **clomiPRAMINE** to a young patient with **obsessive compulsive disorder** and **schizoid personality disorder** [70].

### 3.3.9.A.5] Headache

a) Incidence: 28% to 52% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of headache was 52% with **clomiPRAMINE** (n=322) compared with 41% with placebo (n=319) [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with **obsessive compulsive disorder** (OCD), the incidence of headache was 28% with **clomiPRAMINE** (n=46). However, the incidence was higher in those receiving placebo (34%, n=44) [14].

### 3.3.9.A.6] Impaired cognition

a) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of impaired concentration with **clomiPRAMINE** treatment (n=322) was 5% compared to 2% with placebo (n=319) [14].

b) The effects of a 10-day regimen of **clomiPRAMINE** 25 to 50 mg three times daily on psychomotor and cognitive function were assessed in 12 normal volunteer subjects. **ClomiPRAMINE** had little effect on EEG but reaction speed was markedly slowed. Tolerance did not develop to acute **memory impairment** on a verbal recall test and subjective ratings for mood and bodily symptoms were adversely affected by **clomiPRAMINE** [75].

c) Performance on tasks tapping automatic and voluntary aspects of memory, attention, and motor speed was examined in 14 patients with **major depressive disorder**, before and after 3 weeks of treatment with **clomiPRAMINE** 150 mg/day. Performance on tasks requiring frontal functions improved or did not change, whereas verbal learning and retention, where hippocampal functioning is critical, were impaired. The latter tasks were negatively related to cerebrospinal fluid (CSF) 5-HIAA levels and plasma concentration of **clomiPRAMINE** [76].

### 3.3.9.A.7] Impaired psychomotor performance

a) Performance on tasks tapping automatic and voluntary aspects of memory, attention, and motor speed was examined in 14 patients with **major depressive disorder**, before and after 3 weeks of treatment with **clomiPRAMINE** 150 mg/day. Performance on tasks requiring frontal functions improved or did not change, whereas verbal learning and retention, where hippocampal functioning is critical, were impaired. The latter tasks were negatively related to cerebrospinal fluid (CSF) 5-HIAA levels and plasma concentration of **clomiPRAMINE** [76].

b) The effects of a 10-day regimen of **clomiPRAMINE** 25 to 50 mg three times daily on psychomotor and cognitive function were assessed in 12 normal volunteer subjects. **ClomiPRAMINE** had little effect on EEG but reaction speed was markedly slowed. Tolerance did not develop to acute **memory impairment** on a verbal recall test and subjective ratings for mood and bodily symptoms were adversely affected by **clomiPRAMINE** [75].

### 3.3.9.A.8] Insomnia

a) Incidence: 11% to 25% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of insomnia was 25% with [clomiPRAMINE](#) (n=322) compared with 15% with placebo (n=319) [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of insomnia was 11% with [clomiPRAMINE](#) (n=46) compared with 7% with placebo (n=44) [14].

### 3.3.9.A.9] [Memory impairment](#)

a) Incidence: 7% to 9% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of [memory impairment](#) was 9% with [clomiPRAMINE](#) treatment (n=322) compared with 1% with placebo (n=319) [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of [memory impairment](#) was 7% with [clomiPRAMINE](#) treatment (n=46) compared with 2% with placebo (n=44) [14].

### 3.3.9.A.10] [Myoclonus](#)

a) Incidence: 13% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of myoclonus was 13% with [clomiPRAMINE](#) treatment (n=322) compared with 0% with placebo (n=319) [14].

### 3.3.9.A.11] [Paresthesia](#)

a) Incidence: 9% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of paresthesia was 9% with [clomiPRAMINE](#) treatment (n=322) compared with 3% with placebo (n=319) [14].

### 3.3.9.A.12] [Poor concentration](#)

a) Incidence: 5% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of impaired concentration was 5% with [clomiPRAMINE](#) treatment (n=322) compared with 2% with placebo (n=319) [14].

### 3.3.9.A.13] [Seizure](#)

a) Summary

1) Seizures associated with [clomiPRAMINE](#) have been reported during therapy, upon withdrawal of therapy by patient or neonate, and with overdoses. The Medical Letter



reports that 0.7% of approximately 3,000 patients in United States clinical trials with [clomiPRAMINE](#) have experienced seizures [62].

**2j)** In clinical trials, the observed cumulative incidence of seizures associated with [clomiPRAMINE](#) doses of up to 300 mg/day was 0.64%, 1.12%, and 1.45% at 90 days, 180 days, and 365 days, respectively. The cumulative rates correct the crude rate of 0.7% (25 of 3519 patients) for the variable duration of exposure. Fatalities secondary to seizure have been reported rarely in foreign postmarketing surveillance; some of these cases included concomitant epileptogenic agents or predisposing medical conditions [14].

**3j)** Whether dose or duration of [clomiPRAMINE](#) therapy predicts seizure activity is unknown. Regardless, prescribers are advised to limit the daily dose to a maximum of 250 mg for adults and 3 mg/kg (or 200 mg) in children and adolescents [14].

**bj)** Incidence: 0.7% [14] [62]

**cj)** Several incidences of major motor seizures and [status epilepticus](#) have been reported during clinical trials. The patients had no history of [epilepsy](#) or seizures prior to [clomiPRAMINE](#) therapy. One patient who experienced 2 seizures while on oral [clomiPRAMINE](#) 150 mg/day had a slightly abnormal EEG before treatment began [63]. The other patient experiencing a seizure while on oral [clomiPRAMINE](#) 150 mg/day was withdrawn from the study (Anon, 1986). The patient who experienced [status epilepticus](#) was on oral [clomiPRAMINE](#) 50 mg 3 times a day. The seizures were controlled with anticonvulsants and he was withdrawn from the study [64].

**dj)** A 40-year-old man with no history of [epileptic seizures](#) or [head trauma](#) was admitted to an emergency room comatose with generalized tonic-clonic movements [65]. According to his wife, he had taken approximately 2.5 g (100 tablets each 25 mg) of [clomiPRAMINE](#). Within 8 hours of admission he developed generalized myoclonic jerking. He was treated with [diazepam](#), diuretics, and large volumes of intravenous fluids. Within 4 days the myoclonic attacks resolved and he became fully conscious.

**ej)** Within 36 hours of stopping [clomiPRAMINE](#) 50 mg three times daily, a 67-year-old woman became unconscious and developed clonic contractions of her limbs [66]. Following her convulsion she was restarted on [clomiPRAMINE](#) and fully recovered in 6 weeks, at which time the drug was gradually reduced with no further problems. The patient had no history of [epileptic seizures](#) or [head trauma](#).

**fj)** Two cases of [neonatal convulsions](#) due to maternal withdrawal of [clomiPRAMINE](#) were reported [67]. In the first case a 22-year-old mother had been receiving [clomiPRAMINE](#) at an unspecified dose for the last 7 weeks of pregnancy for depression. She delivered a normal term male infant which developed convulsions at 8 hours of age. Parenteral treatment with [phenobarbital](#) and [paraldehyde](#) did not control the convulsions, which occurred intermittently for 53 hours. In the second case a 38-year-old mother had been receiving [clomiPRAMINE](#) and [flurazepam](#) at unspecified doses throughout pregnancy. Convulsions in the infant began 7 hours after birth. Parenteral [phenobarbital](#) was started but the infant continued to have myoclonic jerks. After 24 hours parenteral [clomiPRAMINE](#) was started at 0.4 mg over 2 hours, which suppressed the convulsions for 11 hours. Twitching in all limbs returned at this time and the infant was started on a continuous infusion of [clomiPRAMINE](#) which was gradually decreased over 12 days. Oral [clomiPRAMINE](#) was started and also slowly decreased. The infant remained jittery but the convulsions were under control. The [clomiPRAMINE](#) was discontinued at day 17 with no ill effects.

**gj)** During a 4-week comparative trial, 36 female patients received either oral [clomiPRAMINE](#) or oral [fluvoxamine](#) 50 mg 3 times daily. During the third treatment week, 1 patient on [clomiPRAMINE](#) developed [status epilepticus](#) that was controlled with anticonvulsants. The patient had no history of [epilepsy](#) and was withdrawn from the study (Klock et al, 1981).



h) Acute and chronic effects of **clomiPRAMINE** on the human EEG in patients treated for depression could not be differentiated [68].

#### 3.3.9.A.14] Serotonin syndrome

a) A 60-year-old woman with depression and anxiety suffered a fatal case of **serotonin syndrome** secondary to her **clomiPRAMINE** treatment. The woman had been receiving **clomiPRAMINE** for 8 months and her dose had been increased to 250 mg daily. Other medication included **lisinopril**, **glyburide**, and **clonazepam**. She became ill over a period of hours and developed **encephalopathy**, myoclonus, hyperreflexia, tremulousness, diarrhea, and incoordination. Her creatine phosphokinase increased to 39,900 units/L. Liver function tests were elevated, **platelet** count was elevated, and her **coagulation studies** were consistent with **disseminated intravascular coagulation**. Her blood level of **clomiPRAMINE** plus the major metabolite was 2,230 nmol/L (normal range less than 1,900). She was treated with cooling blankets, intravenous fluids, **lidocaine** for **ventricular tachycardia**, and **phenytoin** for seizures. **Rhabdomyolysis** occurred resulting in **acute renal failure** and the need for dialysis. After 4 weeks, she developed **opportunistic infections** and died (Rosebush et al, 1999).

b) Sixteen of 38 inpatients with DSM-III-R **major depression** treated with **clomiPRAMINE** alone developed at least one symptom of the **serotonin syndrome** in a prospective study [69]. This syndrome includes confusion, agitation, myoclonus, diaphoresis, tremor, and diarrhea. In 14 cases, tremor and myoclonus occurred simultaneously and 10 patients presented tremor, myoclonus, diaphoresis, and shivering. With the exception of 2 patients, symptoms were transient, lasted less than 1 week, and resolved with treatment.

#### 3.3.9.A.15] Sleep disorder

a) Incidence: 4% to 9% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of sleep disorders was 4% with **clomiPRAMINE** treatment (n=322) compared with 0% with placebo (n=319) [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with **obsessive compulsive disorder** (OCD), the incidence of sleep disorders was 9% with **clomiPRAMINE** treatment (n=46) compared with 5% with placebo (n=44) [14].

#### 3.3.9.A.16] Somnolence

a) Incidence: 46% to 54% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of somnolence was 54% with **clomiPRAMINE** (n=322) compared with 16% with placebo (n=319). Somnolence was the primary reason for discontinuation of treatment [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with **obsessive compulsive disorder** (OCD), the incidence of somnolence was 46% with **clomiPRAMINE** (n=46) compared with 11% with placebo (n=44). Somnolence was the primary reason for discontinuation of treatment [14].

**3.3.9.A.17] Spasmodic movement**

- a) Incidence: 7% [14]
- b) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of twitching was 7% with **clomiPRAMINE** (n=322) compared with 1% with placebo (n=319) [14].

**3.3.9.A.18] Tremor****a) Summary**

- 1) Tremor is a commonly reported adverse effect with **clomiPRAMINE** 75 to 300 mg/day in both depressive and **obsessive compulsive disorder** patients [71] [72] [73] [74].
- b) Incidence: 33% to 54% [14]
- c) Adults

1) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of tremor was 54% with **clomiPRAMINE** (n=322) compared with 2% with placebo (n=319) [14]. In one study, the tremor was rapid with low amplitude and was successfully treated within a few days with oral **biperiden** 6 mg/day [64]

**d) Pediatrics**

1) In placebo-controlled clinical trials of children and adolescents with **obsessive compulsive disorder** (OCD), the incidence of tremor was 33% with **clomiPRAMINE** (n=46) compared with 2% with placebo (n=44) [14].

**3.3.9.A.19] Vertigo**

- a) Incidence: 1% or greater [14]
- b) During premarketing clinical testing of **clomiPRAMINE** in the United States, vertigo was reported on 1 or more occasions in at least 1% of patients (n=3525) [14].

**3.3.10] Ophthalmic Effects****3.3.10.A] Clomipramine Hydrochloride****3.3.10.A.1] Abnormal vision**

- a) Incidence: pediatrics, 7%; adults, 18% [46]
- b) Adult Clinical Trials
  - 1) **Obsessive compulsive disorder** (oral route): 18% vs 4% with placebo [46]
- c) Pediatric Clinical Trials
  - 1) **Obsessive compulsive disorder** (oral route): 7% vs 2% with placebo [46].

**3.3.10.A.2] Angle-closure glaucoma****a) General Information**

1) Pupillary dilation following **clomiPRAMINE** administration may trigger an angle closure attack, particularly in patients with anatomically narrow angles and without a patent **iridectomy** [46].

**b) Prevention and Management**

- 1) Consider examination to determine susceptibility to angle-closure. Prophylactic procedures such as an [iridectomy](#) may be considered in susceptible individuals [46].

**3.3.11] Otic Effects****3.3.11.A] Clomipramine Hydrochloride****3.3.11.A.1] Tinnitus**

- a) Incidence: 4% to 6% [14]  
b) Adults

1) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of tinnitus was 6% with [clomiPRAMINE](#) treatment (n=322) compared with 0% with placebo (n=319) [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of tinnitus was 4% with [clomiPRAMINE](#) treatment (n=46) compared with 0% with placebo (n=44) [14].

**3.3.12] Psychiatric Effects****3.3.12.A] Clomipramine Hydrochloride****3.3.12.A.1] Aggressive behavior**

a) [Paranoid ideation](#) and aggressive behavior developed in two adolescents with [obsessive compulsive disorder](#) during treatment with therapeutic doses of [clomiPRAMINE](#). Possible pathogenetic factors involving serotonin and serotonin receptor abnormalities are discussed [88].

**3.3.12.A.2] Anxiety**

- a) Incidence: 9% [14]  
b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of anxiety was 9% with [clomiPRAMINE](#) treatment (n=322) compared with 4% with placebo (n=319) [14].

**3.3.12.A.3] Delirium**

a) Two women, 61 and 67 years old, whose DSM-IV [major depression](#) failed to respond to oral treatment with [clomiPRAMINE](#) 150 mg/day, developed [delirium](#) and hallucinations when intravenous [clomiPRAMINE](#) 12.5 milligrams was added to the regimen. [Delirium](#) was diagnosed within 4 to 6 days after beginning intravenous administration. In both cases, discontinuation of intravenous administration resulted in gradual improvement, over days, of the delirious state. In both women, plasma levels of [clomiPRAMINE](#) and its metabolite, desmethyldomipramine, doubled with the introduction of intravenous dosing [89].

**3.3.12.A.4] Depression**

- a) Incidence: up to 5% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of depression was 5% with [clomiPRAMINE](#) treatment (n=322) compared with 1% with placebo (n=319) [14].

### 3.3.12.A.5] Hallucinations

a) The onset of "music hallucinations" has been associated with the use of [clomiPRAMINE](#) 75 mg per day three weeks after it was initiated for the treatment of [major depression](#) in a 67-year-old widowed female patient (Valleda & Gentil, 1991).

### 3.3.12.A.6] Mania

a) Mania developed in 6 of 25 patients being treated with [clomiPRAMINE](#) for [unipolar depression](#) (van Sheyen & van Kammen, 1979). The patients had been on oral [clomiPRAMINE](#) 150 to 225 mg/day in 3 divided doses for 6 to 13 weeks before the development of mania. Mania lasted from 15 to 49 days after [clomiPRAMINE](#) was stopped and [perphenazine](#) or [haloperidol](#) therapy was initiated. The duration of the mania strongly correlated with the duration of [clomiPRAMINE](#) therapy.

### 3.3.12.A.7] Panic attack

a) Low-dose (12.5 mg) intravenous [clomiPRAMINE](#) precipitated severe [dysphoria](#)/panic attacks in patients with diagnosed [panic disorder](#) [90].

### 3.3.12.A.8] Suicidal thoughts

#### a) Adult

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, including, [clomiPRAMINE](#) 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 [91].

2) In a pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders including 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in greater than 77,000 patients, the risk of suicidality varied among the drugs studied. However, for almost all drugs studied, there was a tendency toward increasing suicidality in younger patients. The risk difference (drug versus placebo in the number of cases of suicidality per 1000 patients treated) was 14 additional cases in patients less than 18 years of age, 5 additional cases in patients 18 to 24 years, 1 fewer case in patients 25 to 64 years, and 6 fewer cases in patients 65 years and older. No suicides occurred in the pediatric trials. Suicides did occur in the adult trials; however, the number of suicides was insufficient to determine causality [14].

**b) Pediatric**

**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 [92].

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

**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 [92]. Patients should be observed for these symptoms especially during the initial few months of therapy, and at times of dosage increases or decreases [14]

**3.3.12.A.9] Suicide**

**a)** Suicide has been reported in adult patients receiving antidepressant therapy in clinical trials; however, the number of suicides was insufficient to determine causality [14].

**b)** 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, clomipramine 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 [91].

### 3.3.13] Renal Effects

#### 3.3.13.A] Clomipramine Hydrochloride

##### 3.3.13.A.1] Disorder of the urinary system

a) Incidence: 14% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of micturition disorder was 14% with [clomiPRAMINE](#) treatment (n=322) compared with 4% with placebo (n=319) [14].

##### 3.3.13.A.2] Urinary retention

a) Incidence: 7% [14]

b) In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of urinary retention was 7% with [clomiPRAMINE](#) treatment (n=46) compared with 0% with placebo (n=44) [14].

c) A 15-year-old male experienced 2 episodes of urinary retention while on oral [clomiPRAMINE](#) therapy for [obsessive-compulsive disorder](#) [82]. The patient was on [clomiPRAMINE](#) 50 mg 3 times a day and first experienced urinary adverse effects 3 weeks from the initiation of therapy. Subcutaneous [bethanechol](#) 5 mg and oral [phenoxybenzamine](#) 40 mg/day for 3 days failed to improve his symptoms. Improvement in his [obsessive-compulsive behavior](#) was noted throughout [clomiPRAMINE](#) therapy and was maximal when the dose was increased to 200 mg/day. However during week 20 of therapy the patient experienced urinary retention for 16 hours and required [catheterization](#) to remove 1200 mL of urine. Within 8 days of [clomiPRAMINE](#) discontinuation all urinary symptoms had resolved.

##### 3.3.13.A.3] Urinary tract infectious disease

a) Incidence: 6% [14]

b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of [urinary tract infection](#) was 6% with [clomiPRAMINE](#) treatment (n=322) compared with 1% with placebo (n=319) [14].

### 3.3.14] Reproductive Effects

#### 3.3.14.A] Clomipramine

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

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION

#### 3.3.14.B] Clomipramine Hydrochloride

##### 3.3.14.B.1] Disorder of ejaculation

a) Incidence: 6% to 42% [14]

**b) Adults**

**1)** In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of ejaculation failure was 42% with [clomiPRAMINE](#) treatment (n=140) compared with 2% with placebo (n=152) [14].

**2)** Delayed ejaculation has been reported during several studies of patients with [obsessive compulsive disorder](#) at [clomiPRAMINE](#) doses of 50 to 300 mg/day [93] [94] [95].

**3)** Three cases of painful ejaculation associated with [clomiPRAMINE](#) during the first 3 weeks of treatment were reported. Dosage was 100 mg/d in one case and 150 mg/d in 2 cases. The adverse effect resolved within several days of dosage reduction or discontinuation of the medication [96].

**c) Pediatrics**

**1)** In placebo-controlled clinical trials of children and adolescents with [obsessive compulsive disorder](#) (OCD), the incidence of ejaculation failure was 6% with [clomiPRAMINE](#) treatment (n=36) compared with 0% with placebo (n=23) [14].

**3.3.14.B.2] Erectile dysfunction**

**a)** Incidence: 20% [14]

**b)** In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of impotence was 20% with [clomiPRAMINE](#) treatment (n=140) compared with 3% with placebo (n=152) [14].

**3.3.14.B.3] Normal libido, Change in**

**a)** Incidence: 21% [14]

**b)** In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of libido changes was 21% with [clomiPRAMINE](#) treatment (n=322) compared with 3% with placebo (n=319) [14].

**3.3.14.B.4] Orgasm disorder**

**a)** There have been several interesting cases of patients experiencing orgasm when yawning while receiving [clomiPRAMINE](#) therapy. Upon discontinuation of [clomiPRAMINE](#) these symptoms resolved. These side effects were discovered during routine questioning, and no placebo-replacement or rechallenge with [clomiPRAMINE](#) have been tried [97].

**b)** Partial or total [anorgasmia](#) was experienced by 92% (n=24; 17 men and 7 women) of patients with [obsessive compulsive disorder](#) during a double-blind, placebo-controlled study to assess changes in sexual function [98]. None of the 9 placebo patients experienced any sexual dysfunction. Patients received [clomiPRAMINE](#) 25 to 200 mg/day. Most patients still had interest in sex but noticed difficulty in achieving orgasm within the first few days of [clomiPRAMINE](#) therapy. Normal sexual function returned within 3 days of stopping [clomiPRAMINE](#) in all but 1 man who improved without treatment in 3 months.

**c)** Orgasmic inhibition was reported in 1 male and 2 female patients who were depressed with obsessive-compulsive features [99]. [Orgasmic dysfunction](#) occurred shortly after beginning [clomiPRAMINE](#), despite a return of libido as the depression improved. Two patients were switched to [desipramine](#); this resulted in resolution of sexual dysfunction while maintaining depression control. The third patient manipulated the dosing interval and reduced the intensity of the [anorgasmia](#). Strong anticholinergic/antiadrenergic activity is felt to be the cause of [anorgasmia](#) from [clomiPRAMINE](#).



**3.3.14.B.5] Spermatozoa abnormal**

a) Spermogram of 9 patients treated with **clomiPRAMINE** 75 mg/day for 3 months were pathological in terms of volume, motility, and morphology compared with 37% of control patients (same as healthy population). Hormone levels associated with the hypothalamic hypophyseal-gonadal axis were not affected in either group [100].

**3.3.15] Respiratory Effects****3.3.15.A] Clomipramine Hydrochloride****3.3.15.A.1] Bronchospasm**

a) Incidence: 2% to 7% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of **bronchospasm** was 2% with **clomiPRAMINE** treatment (n=322) compared with 0% with placebo (n=319) [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with **obsessive compulsive disorder** (OCD), the incidence of **bronchospasm** was 7% with **clomiPRAMINE** treatment (n=46) compared with 2% with placebo (n=44) [14].

**3.3.15.A.2] Pharyngitis**

a) Incidence: 14% [14]

b) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of **pharyngitis** was 14% with **clomiPRAMINE** treatment (n=322) compared with 9% with placebo (n=319) [14].

**3.3.16] Other****3.3.16.A] Clomipramine Hydrochloride****3.3.16.A.1] Fatigue**

a) Incidence: 35% to 39% [14]

b) Adults

1) In placebo-controlled clinical trials of adult patients with **obsessive compulsive disorder** (OCD), the incidence of fatigue was 39% with **clomiPRAMINE** treatment (n=322) compared with 18% with placebo (n=319) [14].

c) Pediatrics

1) In placebo-controlled clinical trials of children and adolescents with **obsessive compulsive disorder** (OCD), the incidence of fatigue the incidence of was 35% with **clomiPRAMINE** treatment (n=46) compared with 9% with placebo (n=44) [14].

**3.3.16.A.2] Fever**

a) Incidence: 4% [14]



b) In placebo-controlled clinical trials of adult patients with [obsessive compulsive disorder](#) (OCD), the incidence of fever with [clomiPRAMINE](#) treatment (n=322) was 4% compared to 0% with placebo (n=319) [14].

#### 3.3.16.A.3] Withdrawal sign or symptom

a) A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of [clomiPRAMINE](#), including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, [hyperthermia](#), and irritability. In addition, such patients may experience a worsening of psychiatric status. The dosage of [clomiPRAMINE](#) should be gradually tapered and the patient monitored carefully during discontinuation [53] [101].

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

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

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

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

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

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

##### 3) Crosses Placenta: Yes

##### 4) Clinical Management

a) Due to reported [teratogenic effects](#) with other tricyclic antidepressants, use of [clomipramine](#) during pregnancy should be avoided if possible, especially during the first trimester. The dangers of failure to treat [major depression](#), however, are obvious, and in each case these dangers must be weighed against the potential for [teratogenic effects](#).

##### 5) Literature Reports

a) [Clomipramine](#) has not been associated with [teratogenic effects](#) in human case reports, however, other tricyclic antidepressants ([imipramine](#), [amitriptyline](#)) have been associated with [teratogenic effects](#). Neonatal withdrawal symptoms secondary to maternal use of [clomipramine](#) have been reported.

b) Two cases of [neonatal convulsions](#) due to maternal withdrawal of [clomipramine](#) have been reported [555]. In the first case a 22-year-old mother had been receiving [clomipramine](#) at an unspecified dose for the last 7 weeks of pregnancy for depression. She delivered a normal term male infant who developed convulsions at 8 hours of age. Parenteral treatment with [phenobarbital](#) and [paraldehyde](#) did not control the convulsions, which occurred intermittently for 53 hours. In the second case, a 38-year-old mother had been receiving [clomipramine](#) and [flurazepam](#) of

unspecified doses throughout pregnancy. Convulsions in the infant began 7 hours after birth. Parenteral [phenobarbital](#) was started but the infant continued to have myoclonic jerks. After 24 hours parenteral [clomipramine](#) was started at 0.4 mg over 2 hours, which suppressed the convulsions for 11 hours. Twitching in all limbs returned at this time and the infant was started on a continuous infusion of [clomipramine](#) which was started and also slowly decreased. The infant remained jittery but the convulsions were under control. The [clomipramine](#) was discontinued at day 17 with no ill effects.

c) In a case report, a pregnant woman with [endogenous depression](#) had been taking oral [clomipramine](#) 200 mg daily throughout her pregnancy [556]. She delivered an infant who became cyanotic, lethargic, and tachypneic with moderate [respiratory acidosis](#). Treatment with oxygen and incubation reversed these conditions. The infant developed twitches and tremors with an abnormal motor pattern within 24 hours of birth. Following treatment with [phenobarbital](#), the symptoms gradually decreased and completely resolved in one week.

d) A mother treated with [clomipramine](#) during pregnancy delivered a normal infant at term [557]. The newborn did show hypotonia and jitteriness at birth and both effects resolved spontaneously by 6 days of age. The infant was breast-fed while the mother took oral [clomipramine](#) in therapeutic dosage (150 mg/day), producing a [clomipramine](#) level in the infant of 0.4% of the maternal level. Four of five women who took [clomipramine](#) throughout their pregnancies delivered healthy babies with no evidence of [congenital malformations](#). The fifth woman elected to terminate her pregnancy at 9 weeks. Thus, the authors concluded that [clomipramine](#) can be safely used in pregnant women and mothers who breast-feed their newborns without fear of [clomipramine](#) intoxication.

e) Based on data collected through the Motherisk Program, there appear to be no differences in cognitive function, temperament and general behavior in children exposed to [clomipramine](#) throughout gestation as compared to controls [558]. 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 [558].

## B) Breastfeeding

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

2) World Health Organization Rating: Compatible with breastfeeding.

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

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

## 4) Clinical Management

a) According to the American Academy of Pediatrics, [clomipramine](#) is among those agents that may be of concern when used while breastfeeding [559]. Although [clomipramine](#) appears in breast milk, the concentration is low and may not be pharmacologically significant.

## 5) Literature Reports

a)) Clomipramine is excreted in breast milk. A mother treated with clomipramine during pregnancy delivered a normal infant at term [561]. The newborn did show hypotonia and jitteriness at birth and both effects resolved spontaneously by 6 days of age. The milk:plasma ratios on the 4th and 6th days were 1.62 and 1.04, respectively. The infant was started on breastfeeding at the 7th day of age while the mother took oral clomipramine in therapeutic dosage (150 mg/day), producing a clomipramine level in the infant of 0.4% of the maternal level. The milk:plasma ratios on the 10th, 14th, and 35th days were 0.76, 0.84, and 1.22, respectively. The infant remained asymptomatic.

b)) A report describing four women maintained on clomipramine 75 mg to 125 mg per day who breastfed their infants demonstrated that infant serum concentrations of clomipramine metabolites (N-desmethyldomipramine, 8-hydroxydomipramine and 8-hydroxydesmethyldomipramine) were below the assay sensitivity of 10 ng/mL. The measurements were taken after approximately 3 weeks of consistent maternal dosing, and all infants were noted to be developing normally [562].

## 6)) Drug Levels in Breastmilk

### a)) Clomipramine Hydrochloride

#### 1)) Parent Drug

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

1)) 0.76 to 1.62 [561]

#### 2)) Active Metabolites

##### a)) DESMETHYLCLOMIPRAMINE [581]

## 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 [351].

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 [351].

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

### 3.5.1.B] Acenocoumarol

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants [481] [482]. Considerable interindividual differences may be found [483].

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 [478]. 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 [479]. The proposed mechanism of action was 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 [480]. 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.C] 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 [355]. 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 [355]. If concomitant administration is required, monitor the patient closely.

7J) Probable Mechanism: potentiation of vascular effects of [albuterol](#)

#### 3.5.1.D] [Alfuzosin](#)

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

2J) Summary: Both [alfuzosin](#) and [clomipramine](#) have been associated with QT interval prolongation. Use caution when using [alfuzosin](#) and [clomipramine](#) concomitantly due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects [298]. If coadministration is required, monitor closely for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when using [alfuzosin](#) and [clomipramine](#) concomitantly due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects [298]. If coadministration is required, monitor closely for QT interval prolongation.

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

8J) Literature Reports

aJ) In a postmarketing study that evaluated the effect of concomitant administration of [alfuzosin](#) with another QT interval-prolonging drug of similar effect size, the observed QT interval prolongation was greater than that seen with either drug alone, but was not more than additive. The corrected (Fridericia) QT interval (QTcF) increased by 5.9 milliseconds (upper bound of 95% confidence interval (CI), 9.4 milliseconds). The QTcF increase observed with [moxifloxacin](#) 400 mg (positive control) was 10.2 milliseconds (upper bound 95% CI, 13.8 milliseconds). The mean placebo-subtracted QTcF increase following administration of [alfuzosin](#) 10 mg alone was 1.9 milliseconds (upper bound 95% CI, 5.5 milliseconds) [298].

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

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

2J) Summary: Both [clomiPRAMINE](#), a serotonin reuptake inhibitor [14], and [almotriptan](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment and at dosage increases is recommended if [almotriptan](#) and [clomiPRAMINE](#) are used concurrently [387]. 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 [103].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [almotriptan](#) and [clomiPRAMINE](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, monitoring of patient during treatment and dosage increases is recommended [387].

7J) Probable Mechanism: additive serotonergic effect

**3.5.1.F] Amifampridine**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#) [477].
- 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](#) [477].
- 7) Probable Mechanism: additive QT-interval prolongation

**3.5.1.G] Amiodarone**

- 1) Interaction Effect: increased CYP1A2 substrate exposure; increased risk of QT prolongation
- 2) Summary: Avoid coadministration of [amiodarone](#) and this drug as this may result in increased plasma concentrations of the drug and additive effects on the QT interval. Due to the long-half life of [amiodarone](#), this interaction is possible even after discontinuation of [amiodarone](#) [420]. If concomitant use cannot be avoided, consider dosage adjustments and [ECG monitoring](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [amiodarone](#) and this drug should generally be avoided as this may result in increased plasma concentrations of the drug and additive effects on the QT interval. Due to the long-half life of [amiodarone](#), this interaction is possible even after discontinuation of [amiodarone](#) [420]. If concomitant use cannot be avoided, consider dosage adjustments and [ECG monitoring](#).
- 7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism by [amiodarone](#); additive effects on QT interval

**3.5.1.H] Amitriptyline**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [amitriptyline](#) and [clomiPRAMINE](#) is not common clinical practice. However if using [amitriptyline](#) and [clomiPRAMINE](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [102]. Additionally, caution is advised when using [amitriptyline](#), a CYP2D6 substrate, with [clomiPRAMINE](#), a CYP2D6 substrate and inhibitor. Consideration should be given to monitoring both [amitriptyline](#) and [clomiPRAMINE](#) levels [14] [102].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [amitriptyline](#) and [clomiPRAMINE](#) is not common clinical practice. However if using [amitriptyline](#) and [clomiPRAMINE](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [102]. Additionally, caution is advised when using [amitriptyline](#), a CYP2D6 substrate, with [clomiPRAMINE](#), a CYP2D6 substrate and inhibitor. Monitoring of both [amitriptyline](#) and [clomiPRAMINE](#) levels should be considered [14] [102].
- 7) Probable Mechanism: additive effects on the QT interval



**3.5.1.I] 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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.J] Amoxapine**

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

2) Summary: Postmarketing cases of ECG abnormalities and [arrhythmia](#) have been infrequently reported with [clomiPRAMINE](#) [14]. While the concomitant use of [amoxapine](#) and [clomiPRAMINE](#) is not common clinical practice, if required, use caution due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiovascular effects.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [amoxapine](#) and [clomiPRAMINE](#) is not common clinical practice. However, if using [amoxapine](#) and [clomiPRAMINE](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.

7) Probable Mechanism: additive effects on the QT interval

**3.5.1.K] Amphetamine**

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in

blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

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



- 1) Interaction Effect: increased tricyclic serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: Coadministered [amprenavir](#) may increase serum concentrations of tricyclic antidepressants, causing a potential risk of [arrhythmias](#) or other serious adverse effects. Currently no interaction study has been conducted. Amprenavir is metabolized by cytochrome P450 3A4 enzymes in addition to being a CYP3A4 inhibitor, and tricyclics may partially depend on this pathway for metabolism. Plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly in patients also receiving [amprenavir](#) [408].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: If concomitant therapy with [amprenavir](#) and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#)).
- 7) Probable Mechanism: inhibition of cytochrome P450-mediated tricyclic metabolism

#### 3.5.1.M] [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](#) [403].
- 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](#) [403].
- 7) Probable Mechanism: additive effects on the QT interval

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

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants [462] [463]. Considerable interindividual differences may be found [464].
- 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 [459]. 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 [460]. 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 [461]. 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.O] [Apomorphine](#)

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

2)) Summary: Concomitant use of [apomorphine](#) and [clomipRAMINE](#) may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#). Therefore, caution should be used when these agents are given concurrently [136], and closely monitor for QT interval prolongation.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [apomorphine](#) and [clomipRAMINE](#) may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#). Therefore, caution should be used when these agents are given concurrently [136] and closely monitor for QT interval prolongation.

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

### 3.5.1.P] [Aprobarbital](#)

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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.Q] [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 [426].
- 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.R] [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 [425]. 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 [425].
- 7) Probable Mechanism: potentiation of cardiovascular effects

#### 3.5.1.S] [Aripiprazole](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation [526], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation [526], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.T] Armodafinil

- 1) Interaction Effect: increased [clomiPRAMINE](#) exposure
- 2) Summary: Administration of armodafinil (R-enantiomer of [modafinil](#)) may cause moderate inhibition of CYP2C19 isozyme activity. Although not studied with [clomiPRAMINE](#), a CYP2C19 substrate, concurrent administration of a single 400-mg dose of armodafinil with a 40-mg dose of [omeprazole](#), also a CYP2C19 substrate, led to an approximately 40% increase in systemic exposure of [omeprazole](#). Additionally, increased levels of [clomiPRAMINE](#) and its active metabolite, desmethylclomipramine, were reported in a narcoleptic patient receiving concomitant therapy with [modafinil](#). Therefore, use caution when armodafinil and [clomiPRAMINE](#) are used concurrently. Dose reductions of [clomiPRAMINE](#) may be necessary [105]. Also, monitor patients for increased [clomiPRAMINE](#) adverse events (dry mouth, sedation, urinary retention).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the coadministration of armodafinil and [clomiPRAMINE](#) as this may result in increased [clomiPRAMINE](#) exposure. Dose reductions of [clomiPRAMINE](#) may be necessary [105]. Monitor patients for increased [clomiPRAMINE](#) adverse events (dry mouth, sedation, urinary retention).
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [clomiPRAMINE](#) metabolism

### 3.5.1.U] Arsenic Trioxide

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Arsenic trioxide](#) is known to prolong the QT interval and may result in [complete atrioventricular block](#) and/or [ventricular arrhythmias](#), including [torsade de pointes](#). Although this interaction has not been evaluated, the concomitant use of [arsenic trioxide](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), may increase the risk of prolonged QT interval and [ventricular arrhythmias](#). When possible, [clomiPRAMINE](#) therapy should be discontinued prior to [arsenic trioxide](#) treatment [309]; however, if coadministration is required, monitor for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on the QT interval, caution is advised if [arsenic trioxide](#) is given concurrently with other drugs that prolong the QT interval, such as [clomiPRAMINE](#). When possible, [clomiPRAMINE](#) therapy should be discontinued prior to [arsenic trioxide](#) treatment [309]. If coadministration is required, monitor for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.V] Artemether

- 1) Interaction Effect: an increased risk of QT-interval prolongation
- 2) Summary: Avoid concomitant use of artemether/lumefantrine and [clomiPRAMINE](#) due to the additive risk of QT-interval prolongation. Coadministration of artemether/lumefantrine, a CYP2D6 inhibitor, with [clomiPRAMINE](#), a CYP2D6 substrate, may significantly increase the plasma concentration of [clomiPRAMINE](#) and further increase the risk of QT-interval prolongation or other serious adverse effects. If concurrent administration of artemether/lumefantrine and [clomiPRAMINE](#) is medically required, use caution and monitor the ECG. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [181].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of artemether/lumefantrine and [clomiPRAMINE](#) due to the additive risk of QT-interval prolongation or other serious adverse effects. If concurrent administration of artemether/lumefantrine and [clomiPRAMINE](#) is medically required, use caution and monitor the ECG. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [181].
- 7) Probable Mechanism: additive effects on QT-interval prolongation; inhibition of CYP2D6-mediated metabolism of [clomiPRAMINE](#)

### 3.5.1.W] Asenapine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Avoid using asenapine and [clomiPRAMINE](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events. Additionally, asenapine is a weak CYP2D6 inhibitor and [313] [clomiPRAMINE](#) is a CYP2D6 substrate. Monitoring plasma levels of [clomiPRAMINE](#) may be warranted with used in combination with CYP2D6 inhibitors [14].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid using asenapine and [clomiPRAMINE](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events [313].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.X] Astemizole

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Due to the potential for additive effects on the QT interval and risk of serious cardiac adverse events, use caution with the coadministration of [astemizole](#) and other drugs that may prolong the QT interval, such as [clomiPRAMINE](#). If concomitant use is required, closely monitor for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when [astemizole](#) is coadministered with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), as this may result in additive effects of QT interval prolongation and an increased risk of serious cardiac events. If concomitant use is required, monitor for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.Y] Atazanavir

- 1) Interaction Effect: increased plasma concentrations of tricyclic antidepressants (drowsiness, hypotension, [akathisia](#))
- 2) Summary: Coadministration of [atazanavir](#) and tricyclic antidepressants has not been studied. However, the coadministration of [atazanavir](#) and tricyclic antidepressants has the potential to produce serious and/or life-threatening adverse events [389].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: If [atazanavir](#) and tricyclic antidepressants are used concomitantly, monitor patient for clinical signs and symptoms of tricyclic antidepressant toxicity (hypotension, [akathisia](#), anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#)).

7) Probable Mechanism: unknown

### 3.5.1.Z] [Atomoxetine](#)

1) Interaction Effect: an increase in [atomoxetine](#) steady-state plasma concentrations

2) Summary: [Atomoxetine](#) is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, [atomoxetine](#) steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as [clomipramine](#). The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with [clomipramine](#), the area under the concentration-time curve of [atomoxetine](#) is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than [atomoxetine](#) alone [338].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Dosage adjustment of [atomoxetine](#) may be necessary when coadministered with [clomipramine](#).

7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of [atomoxetine](#) by [clomipramine](#)

### 3.5.1.AA] [Azithromycin](#)

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

2) Summary: Similar to some other macrolides, [azithromycin](#) may prolong the QT interval [314]. Although the interaction has not been evaluated, the concomitant use of [azithromycin](#) with other drugs that may prolong the QT interval, such as [clomipramine](#), may result in an increased risk of QT interval prolongation. If concomitant use is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The coadministration of [azithromycin](#) with other drugs that may prolong the QT interval, such as [clomipramine](#), may result in additive effects on QT interval prolongation. If concomitant use is required, use caution and monitor for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

### 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 [118]. 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 [118]. 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] [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 [307], 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 [307], as coadministration may increase the risk of [ventricular arrhythmias](#).

7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.AE] [Bethanidine](#)

1) Interaction Effect: decreased antihypertensive effectiveness

2) Summary: 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 [143] [144] [145].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The combination of bethanidine and [clomiPRAMINE](#), as well as other tricyclic antidepressant agents, should be avoided. An alternative antihypertensive agent 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 2 of 8 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 antidepressant therapy in several patients resulted in postural hypotension that necessitated a reduction in dosage of bethanidine or debrisoquine [142].

### 3.5.1.AF] [Bromocriptine](#)

- 1)) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2)) Summary: Both [bromocriptine](#), a serotonergic agonist, and [clomiPRAMINE](#), a serotonin reuptake inhibitor, may cause [serotonin syndrome](#). Concomitant use should be approached with caution [14] 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 [bromocriptine](#) and [clomiPRAMINE](#) are used concurrently.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution with concomitant administration of [bromocriptine](#) and [clomiPRAMINE](#), a serotonin reuptake inhibitor [14], 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.AG] [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 [120].
- 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 [120].
- 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 [121].

**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](#) [122].

### 3.5.1.AH] 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 [504] [505] [506]. 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 [504] [505] [506].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AI] 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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.AJ] [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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.AK] [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 [148] [149].
- 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.

- 7J) Probable Mechanism: possibly due to beta-adrenergic effect of cannabis coupled with the anticholinergic effect of tricyclic antidepressants
- 8J) Literature Reports

aJ) 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 [146].

bJ) 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, and 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](#) [147].

### 3.5.1.ALJ [Carbamazepine](#)

- 1J) Interaction Effect: decreased [clomiPRAMINE](#) effectiveness
- 2J) Summary: The concomitant use of [carbamazepine](#) and antidepressants has been reported to decrease antidepressant levels [295] [296]. Although not reported for [clomiPRAMINE](#), a similar interaction could occur.
- 3J) Severity: moderate
- 4J) Onset: delayed
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Monitor for clinical efficacy of the [clomiPRAMINE](#) 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.
- 7J) Probable Mechanism: increased [clomiPRAMINE](#) metabolism
- 8J) Literature Reports

aJ) Concomitant administration of [imipramine](#) and [carbamazepine](#) to children with [attention deficit disorder](#) (ADD) has been reported to result in a 50% decrease in the total plasma concentration of [imipramine](#) plus [desipramine](#) [293]. [Carbamazepine](#) enhances the hepatic microsomal metabolism of [imipramine](#) and other tricyclic antidepressants by inducing hepatic enzymes [294]. Although not reported specifically for [clomiPRAMINE](#), be aware that the potential for a similar interaction exists. Patients on chronic [carbamazepine](#) therapy may require increased doses of tricyclic antidepressants.

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

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Postmarketing cases of ECG changes have been reported with [chloroquine](#) use [315] and abnormal ECG and [arrhythmia](#) have been reported with [clomiPRAMINE](#) use [14]. Although this interaction has not been evaluated, the concomitant use of [chloroquine](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), may increase the risk of QT interval prolongation. If coadministration is required, monitoring for QT prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the concomitant use of [chloroquine](#) and drugs that may prolong the QT interval, such as [clomiPRAMINE](#), due to increased risk of additive QT interval prolongation. If coadministration is required, monitor for QT prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.AN] [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 [226], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [227]. The effects of the interaction appear to be estrogen dose-related [228] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [229].
- 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) The qualitative effects of concomitant administration of estrogen and TCAs was evaluated. 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 [217].

- b)) A case reported demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams [218]. 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 [219].
- c)) A study in which women received [clomiPRAMINE](#) and oral contraceptives or [clomiPRAMINE](#) alone was reviewed. 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 [220].
- d)) The effects of oral contraceptives on [clomiPRAMINE](#) in 42 women between the ages of 18 and 40 was studied. 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 [221].
- e)) [Akathisia](#) in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently was reported. 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 [222].
- 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 [223].
- g)) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [224]. 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 [225].

**3.5.1.AO] Chlorpromazine**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Both [chlorproMAZINE](#) and [clomiPRAMINE](#) may prolong the QT interval [388] [14] and concomitant use of these agents may increase the risk of serious cardiac events. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Both [chlorproMAZINE](#) and [clomiPRAMINE](#) may prolong the QT interval [388] [14] and concomitant use of these agents may increase the risk of serious cardiac events. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

**3.5.1.AP] Cimetidine**

- 1) Interaction Effect: [clomiPRAMINE](#) toxicity (dry mouth, blurred vision, urinary retention)
- 2) Summary: [Cimetidine](#) impairs the metabolism of tricyclic antidepressants [150] [151] [152]. Although not reported for [clomiPRAMINE](#), it is likely that a similar interaction would occur because of the mechanism involved.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Consider monitoring 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 [clomiPRAMINE](#) metabolism

**3.5.1.AQ] Cinacalcet**

- 1) Interaction Effect: increased [clomiPRAMINE](#) 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 [clomiPRAMINE](#) are coadministered, dose adjustments of [clomiPRAMINE](#) may be required [352]. Monitoring of [clomiPRAMINE](#) plasma concentrations is recommended during the concomitant use of [clomiPRAMINE](#) with a CYP2D6 inhibitor, such as [cinacalcet](#). Dose adjustments of one or both drugs, especially during therapy initiation and discontinuation, may be warranted [14].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: If [cinacalcet](#) is coadministered with a tricyclic antidepressant (TCA), such as [clomiPRAMINE](#), a dose reduction of the TCA may be necessary [352]. Monitoring of [clomiPRAMINE](#) plasma concentrations is recommended during the concomitant use of [cinacalcet](#) with [clomiPRAMINE](#). Dose adjustments of one or both drugs, especially during therapy initiation and discontinuation, may be warranted [14].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [clomiPRAMINE](#) metabolism by [cinacalcet](#)

**3.5.1.AR] Ciprofloxacin**



- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [ciprofloxacin](#) and [clomiPRAMINE](#) may increase the risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)) and should be undertaken with caution. Geriatric patients may be particularly sensitive to QT prolongation [117]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [ciprofloxacin](#) and [clomiPRAMINE](#) may increase the risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)) and should be undertaken with caution. Geriatric patients may be particularly sensitive to QT prolongation [117]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AS] [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](#) [333].
- 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](#) [333].
- 7) Probable Mechanism: additive QT-interval prolongation

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

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [citalopram](#) and [clomiPRAMINE](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant use is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [312]. Additionally, caution is advised when using [clomiPRAMINE](#), a CYP2D6 substrate, with [citalopram](#), a weak CYP2D6 inhibitor. It is advisable to monitor [clomiPRAMINE](#) concentrations whenever a CYP2D6 inhibitor is used concurrently. Lower doses of [clomiPRAMINE](#) or [citalopram](#) may be necessary [14].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [citalopram](#) and [clomiPRAMINE](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant use is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [312]. Additionally, caution is advised when using [clomiPRAMINE](#), a CYP2D6 substrate, with [citalopram](#), a weak CYP2D6 inhibitor. Consider monitoring [clomiPRAMINE](#) concentrations and use lower doses of [clomiPRAMINE](#) or [citalopram](#), if necessary [14].
- 7) Probable Mechanism: additive effects on QT interval prolongation



**3.5.1.AU] Clarithromycin**

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Postmarketing cases of abnormal ECG and [arrhythmia](#) have been reported with [clomiPRAMINE](#) use [14] and QT prolongation and [ventricular arrhythmias](#), including [ventricular tachycardia](#) and [torsade de pointes](#), have been reported with [clarithromycin](#) [332]. Although this interaction has not been evaluated, the concomitant use of [clarithromycin](#) with [clomiPRAMINE](#) may increase the risk of QT interval prolongation and [torsade de pointes](#). If coadministration is required, monitoring for QT prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the concomitant use of [clarithromycin](#) and other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), as concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, monitor for QT prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.AV] Clobazam**

- 1) Interaction Effect: increased [clomiPRAMINE](#) plasma concentrations
- 2) Summary: The concomitant use of [clomiPRAMINE](#), a CYP2D6 substrate [14], and clobazam, a CYP2D6 inhibitor, may increase [clomiPRAMINE](#) plasma concentrations. Dose reduction of [clomiPRAMINE](#) may be required when coadministered with clobazam [183]. If clobazam therapy is withdrawn, a higher dose of [clomiPRAMINE](#) may be necessary [14].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of clobazam with [clomiPRAMINE](#) may cause increased [clomiPRAMINE](#) plasma concentrations. If concomitant use is required, dose reduction may be warranted for [clomiPRAMINE](#) [183]. If clobazam therapy is withdrawn, a higher dose of [clomiPRAMINE](#) may be necessary [14].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [clomiPRAMINE](#) metabolism by clobazam

**3.5.1.AW] Clonidine**

- 1) Interaction Effect: decreased antihypertensive effectiveness
- 2) Summary: Concomitant [clonidine](#) and tricyclic antidepressant (TCA) therapy may impair the antihypertensive effects of [clonidine](#) [470]. 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 [471] [472] [473] [474]. Mianserin, a tetracyclic antidepressant, was not shown to exhibit the impairment of [clonidine's](#) antihypertensive effects seen with tricyclic antidepressants [475] [476].
- 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](#) developed 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 [467].

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 [468].

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 [469].

### 3.5.1.AX] [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 [334]. 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 [334]. 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 [335].

b) Serum concentrations of [clozapine](#) and nortoclozapine, the major metabolite, were evaluated when given in combination with the SSRIs [fluoxetine](#), [paroxetine](#), and [sertraline](#). Eighty

outpatients receiving [clozapine](#) all had been diagnosed with [schizophrenia](#) or major affective disorder, and 40 of these patients were receiving an SSRI in combination with [clozapine](#). Of these 40 patients, 14 were receiving [fluoxetine](#), 10 were receiving [sertraline](#), and 16 were receiving [paroxetine](#) therapy. Among the patients on SSRI therapy, serum concentrations of [clozapine](#) and nortriptyline were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of [clozapine](#) plus nortriptyline concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating [clozapine](#) impaired clearance. The differences between the 3 SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs [336].

### 3.5.1.AY] Cobicistat

- 1) Interaction Effect: increased plasma concentrations of [clomipramine](#)
- 2) Summary: Concurrent use of [clomipramine](#), a CYP2D6 substrate [156], together with cobicistat, an inhibitor of CYP2D6 [258], may lead to increased concentrations of [clomipramine](#). If concurrent therapy is necessary, carefully titrate the dose of [clomipramine](#) and monitor for antidepressant response [258]. In addition, consider measuring [clomipramine](#) plasma concentrations. Lower doses of [clomipramine](#) may be required and if cobicistat is discontinued, an increase in the dose of [clomipramine](#) may be necessary [156].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [clomipramine](#) and cobicistat may lead to increased concentrations of [clomipramine](#). If coadministration is necessary, carefully titrate the dose of [clomipramine](#) and monitor for antidepressant effect [258]. Also, consider monitoring [clomipramine](#) plasma concentrations. Lower doses of [clomipramine](#) may be required and if cobicistat is discontinued, an increase in the dose of [clomipramine](#) may be necessary [156].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [clomipramine](#) by cobicistat

### 3.5.1.AZ] 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 [518], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [519]. The effects of the interaction appear to be estrogen dose-related [520] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [521].
- 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 [509].

**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 [510] [511].

**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 [512].

**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 [513].

**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 [514].

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 [515].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [516]. 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 [517].

### 3.5.1.BA] 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 [137]. 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 [137]. Dose reduction of crizotinib may be warranted.

7) Probable Mechanism: additive effects on QT interval

### 3.5.1.BB] 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 [179] [180].

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 [179] [180].

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.BC] 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 [394]. 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 [394]. Exercise caution with concomitant use and consider assessment and periodic monitoring for [ventricular arrhythmia](#).
- 7) Probable Mechanism: additive QT prolongation

#### 3.5.1.BD| [Darunavir](#)

- 1) Interaction Effect: SSRI effects unknown; increased tricyclic antidepressant exposure
- 2) Summary: Use caution with coadministration of [darunavir](#) with antidepressants (ie, SSRIs, tricyclic antidepressants, or [trazodone](#)). If coadministered, carefully titrate the antidepressant to the desired effect. Use the lowest effective antidepressant dose and monitor antidepressant response with concurrent use [349].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [darunavir](#) with antidepressants (ie, SSRIs, tricyclic antidepressants, or [trazodone](#)). If coadministered, carefully titrate the antidepressant to the desired effect. Use the lowest effective antidepressant dose and monitor antidepressant response with concurrent use [349].
- 7) Probable Mechanism: unknown

#### 3.5.1.BE| [Dasatinib](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [clomipRAMINE](#) and [dasatinib](#) concomitantly due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular events [331].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [clomipRAMINE](#) and [dasatinib](#) concomitantly due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular events [331].
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.BF| [Deferasirox](#)

- 1) Interaction Effect: increased CYP1A2 substrate exposure
- 2) Summary: Concomitant administration of [deferiasirox](#), a CYP1A2 inhibitor, with a single dose of [theophylline](#), a CYP1A2 substrate, resulted in an approximate doubling of the [theophylline](#) AUC and elimination half-life in healthy volunteers. Use caution if [deferiasirox](#) is coadministered with drugs that are metabolized by CYP1A2, such as [amitriptyline](#), [naproxen](#), or [triamterene](#), as similar increases in plasma



concentration may be expected. If [deferasirox](#) and CYP1A2 substrates are coadministered, monitoring of patients for exposure related toxicity is recommended [364].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [deferasirox](#), a CYP1A2 inhibitor, with drugs that are metabolized by CYP1A2, such as [acetaminophen](#), [clomipramine](#), or [naproxen](#), may lead to increased plasma concentrations of the CYP1A2 substrate. If coadministration is required, monitor for patients for exposure related toxicity [364].

7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism by [deferasirox](#)

### 3.5.1.BG] 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 [504] [505] [506]. 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 [504] [505] [506].

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BH] 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 [265].

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 [265].

7) Probable Mechanism: additive QT- interval prolongation

### 3.5.1.BI] Desipramine

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

2) Summary: [Desipramine](#) may prolong the QT interval at very high doses [507], and use with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), may result in additive effects on QT interval prolongation. Concomitant use of [desipramine](#) and [clomiPRAMINE](#) is not common in clinical practice. However, if coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major



- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [clomiPRAMINE](#) and [desipramine](#) is not common clinical practice. However, if using [clomiPRAMINE](#) and [desipramine](#) (especially at high doses [507]) concomitantly, use caution due to the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.BJ] 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 [504] [505] [506]. 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 [504] [505] [506].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BK] Desogestrel

- 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: probable
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes
- 8) Literature Reports

a) 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 [231].

**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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants (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 effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

**e)** [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 [236].

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 [237].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.BLJ 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 [153].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with coadministration of desvenlafaxine (a weak CYP2D6 inhibitor and serotonergic agent) with serotonergic drugs that are also CYP2D6 substrates. Coadministration may result in additive serotonergic effects and may increase CYP2D6 substrate exposure. If concurrent use is required, CYP2D6 substrates may be given at the recommended dose when coadministered with desvenlafaxine 100 mg/day or less. Reduce the CYP2D6 substrate dose by 50% if using concurrently with desvenlafaxine 400 mg/day (unapproved dosing); increase the CYP2D6 substrate to the original dose if concurrent desvenlafaxine 400 mg/day is discontinued. Careful monitoring for signs and symptoms of [serotonin syndrome](#) is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops [153].

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

8) Literature Reports

a) Coadministration of [desipramine](#) (a CYP2D6 substrate) 50 mg with desvenlafaxine 400 mg/day (unapproved dosing) in a clinical study resulted in an increase of approximately 50% for the C<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) [153].

### 3.5.1.BM] Dexfenfluramine

- 1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of

depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.BN] **Dexmethylphenidate**

- 1) Interaction Effect: **hypertension**, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and **amphetamine** administration has been reported to result in enhanced **amphetamine** effects from the release of **norepinephrine** [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When **amphetamine** analogs are being used to treat **obesity**, it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for **amphetamines** have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (**hypertension** and **dysrhythmias**).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of **amphetamines** and tricyclic antidepressants or other sympathomimetic agents could lead to **hypertension**, increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for **hypertension** and **dysrhythmias**.
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports

a) **Amphetamines** may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as **desipramine** or **protriptyline** results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that **methylphenidate** may inhibit the metabolism of some tricyclic antidepressants, such as **imipramine**, **clomipramine**, or **desipramine** [376].

c) A 55-year-old female patient was maintained on **imipramine** 350 mg daily for several years, with **imipramine** plus **desipramine** blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with **fenfluramine** 20 mg three times daily, the patient fell asleep while driving. The **imipramine** plus **desipramine** level was 704 mcg/L. **Fenfluramine** may have inhibited the CYP450 isoenzyme responsible for metabolizing **imipramine** [377].

d) Concomitant administration of tricyclic antidepressants and **methylphenidate** can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the **methylphenidate** usually results in the blood pressure returning to normotensive levels; reinstitution of the **methylphenidate** resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III **major depression**, who failed to respond to treatment with **desipramine** given for at least four weeks, were given **fenfluramine** 40 mg to 120 mg daily for two

weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

**f)** There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

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

**1)** Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

**2)** Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: theoretical

**6)** Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

**7)** Probable Mechanism: synergistic effects on noradrenergic neurotransmission

**8)** Literature Reports

**a)** [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

**b)** Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

**c)** A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

**d)** Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation



of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

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

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

2) Summary: The concomitant use of [dextromethorphan](#) and a tricyclic antidepressant (such as [clomipramine](#)) may result in an increased risk of [serotonin syndrome](#). While not specifically studied with [clomipramine](#), 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 [522]. If both [clomipramine](#) 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 [clomipramine](#)), as concomitant use may result in an increased risk of [serotonin syndrome](#) [522].

7) Probable Mechanism: additive CNS serotonin concentrations

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

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants [449] [450]. Considerable interindividual differences may be found [451].

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 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 [446]. 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 [447]. 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 [448]. 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.BR] [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 [211], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [212]. The effects of the interaction appear to be estrogen dose-related [213] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [214].

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

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 [202].

- 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 [203]. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [204].
- 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 [205].
- 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 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 [206].
- e)** [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 [207].
- 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 [208].
- g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [209]. 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 [210].

**3.5.1.BS] Dienogest**

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

**2)** Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable

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

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

**8)** Literature Reports

**a)** 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 [231].

**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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant (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 effects of oral contraceptives on **clomiPRAMINE** were 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 [235].

**e)** **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 [236].

**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 [237].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (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.BT] **Diethylpropion**

**1)** Interaction Effect: **hypertension**, other cardiac effects, and CNS stimulation

**2)** Summary: Concomitant tricyclic antidepressant (TCA) and **amphetamine** administration has been reported to result in enhanced **amphetamine** effects from the release of **norepinephrine** [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When **amphetamine** analogs are being used to treat **obesity**, it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for **amphetamines** have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (**hypertension** and **dysrhythmias**).

**3)** Severity: moderate

- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.BU] [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 [198], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [199]. The effects of the interaction appear to be estrogen dose-related [200] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [201].



- 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 [189].

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 [190]. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [191].

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 [192].

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 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 [193].

e) **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 [194].

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 [195].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [196]. 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 [197].

### 3.5.1.BV] **Diphenhydramine**

- 1) Interaction Effect: increased anticholinergic effects (dry mouth, urinary retention)
- 2) Summary: Concomitant antidepressants with strong anticholinergic effects (e.g., **amitriptyline**, **amoxapine**, **clomiPRAMINE**) and antihistamines may increase the possibility of **adynamic ileus**, urinary retention, or chronic **glaucoma**. This interaction may be more prominent in elderly patients [493] [494].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Patients should be warned that taking antihistamines, including over-the-counter sleeping pills and cold and allergy preparations, may increase the side effects of **clomiPRAMINE**. Patients should be monitored for dry mouth, drowsiness, and problems with urination. Lower dose of **diphenhydrAMINE** might be considered, particularly in elderly individuals.
- 7) Probable Mechanism: additive anticholinergic effects

### 3.5.1.BW] **Disopyramide**

- 1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsades de pointes**, **cardiac arrest**)
- 2) Summary: Concomitant use of tricyclic antidepressants, including **clomiPRAMINE**, and class IA antiarrhythmics, including **disopyramide**, may increase the risk of **cardiotoxicity** due to similar cardiac effects of these drugs [125] [126]. Therefore, monitoring the patient for signs and symptoms of **cardiac toxicity** during coadministration of **clomiPRAMINE** and **disopyramide** may be warranted.
- 3) Severity: major
- 4) Onset: unspecified



5) Substantiation: theoretical

6) Clinical Management: Concomitant use of **clomiPRAMINE** and **disopyramide** may increase the risk of **cardiotoxicity** (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs [125] [126]. 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** [127].

### 3.5.1.BX] **Dofetilide**

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

2) Summary: Due to the potential for additive effects on the QT interval and increased risk of serious cardiac effects, concomitant use of **dofetilide** with other drugs that may prolong the QT interval, such as **clomiPRAMINE**, is not recommended [330]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of **dofetilide** with other drugs that may prolong the QT interval, such as **clomiPRAMINE**, is not recommended due to the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [330]. If coadministration is required, monitor for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval

### 3.5.1.BY] **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 [112] [113].

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 [112] [113].

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

### 3.5.1.BZ] Domperidone

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: ECG abnormalities and [arrhythmias](#) have been reported with [clomiPRAMINE](#) use [14], therefore use caution with coadministration of [clomiPRAMINE](#), a potential QT prolonging drug, and domperidone, a drug that has been associated with an increased risk of sudden cardiac death. In case control studies, an increase risk of sudden cardiac death was observed with the use of oral domperidone, particularly at doses greater than 30 mg/day and in patients older than 60 years of age. If coadministration is necessary, domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [508].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when coadministering [clomiPRAMINE](#) and domperidone as this may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#) and sudden cardiac death, particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years. If coadministration is necessary, domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [508].

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CA] Donepezil

1) Interaction Effect: lower seizure threshold

2) Summary: Seizure threshold lowering effects have been associated with [donepezil](#) [111]. Use extreme caution when prescribing [donepezil](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Seizure threshold lowering effects have been associated with [donepezil](#) [111]. Use extreme caution when prescribing [donepezil](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.

7) Probable Mechanism: unknown

### 3.5.1.CB] 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](#) [264].

- 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](#) [264].
- 7) Probable Mechanism: additive QT-interval prolongation

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

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Both [clomiPRAMINE](#) and [droperidol](#) may prolong the QT interval. Concomitant use of [droperidol](#) and [clomiPRAMINE](#) may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#). Therefore, concomitant use should be avoided. If coadministration is required, consider [monitoring ECGs](#) (prior to treatment and 2 to 3 hours after completing [droperidol](#)) and evaluating electrolyte (ie, magnesium, potassium) levels [340].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the concomitant use of [droperidol](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), as coadministration may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#). If concomitant use is required, monitor ECGs (prior to treatment and 2 to 3 hours after completing [droperidol](#)) and evaluate electrolyte (ie, magnesium, potassium) levels [340].
- 7) Probable Mechanism: additive effects on the QT interval

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

- 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: probable
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes
- 8) Literature Reports

a) 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 [231].

**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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants (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 effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

**e)** [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 [236].

**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 [237].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (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.CE] [Duloxetine](#)

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

**2)** 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 [114].

**3)** Severity: moderate

**4)** Onset: unspecified

**5)** Substantiation: theoretical

**6)** 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 [114]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).

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

### 3.5.1.CF] [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 [405].

**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 [405].

**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 [405].

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

- 1) Interaction Effect: [clomiPRAMINE](#) toxicity (confusion, insomnia, irritability)
- 2) Summary: The addition of [clomiPRAMINE](#) to long-standing [enalapril](#) therapy resulted in high blood levels of [clomiPRAMINE](#) and signs of toxicity (confusion, insomnia, irritability, and mood changes) in 2 cases. Reduction of the [clomiPRAMINE](#) dose resulted in lower blood levels [466].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for signs of [clomiPRAMINE](#) toxicity; lower doses may be required with concurrent therapy with [enalapril](#).
- 7) Probable Mechanism: unknown

### 3.5.1.CH| [Enalapril Maleate](#)

- 1) Interaction Effect: [clomiPRAMINE](#) toxicity (confusion, insomnia, irritability)
- 2) Summary: The addition of [clomiPRAMINE](#) to long-standing [enalapril](#) therapy resulted in high blood levels of [clomiPRAMINE](#) and signs of toxicity (confusion, insomnia, irritability, and mood changes) in 2 cases. Reduction of the [clomiPRAMINE](#) dose resulted in lower blood levels [466].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for signs of [clomiPRAMINE](#) toxicity; lower doses may be required with concurrent therapy with [enalapril](#).
- 7) Probable Mechanism: unknown

### 3.5.1.CI| [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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [167] [168] [169] [170].
- 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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [165].

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 [166].

### 3.5.1.CJ] Erythromycin

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

2)) Summary: The concomitant use of erythromycin with other drugs that may prolong the QT interval, such as clomiPRAMINE, should be approached with caution due to the potential for additive effects on QT interval prolongation and an increased risk of torsade de pointes [341]. If concomitant therapy is required, closely monitor for QT interval prolongation.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution with the concomitant use of erythromycin and other drugs that may prolong the QT interval, such as clomiPRAMINE, as this may increase the risk of cardiac adverse events, including torsade de pointes [341]. If concomitant therapy is required, monitor for QT prolongation.

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

### 3.5.1.CK] Escitalopram

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

2)) Summary: Escitalopram is a QT-interval-prolonging drug [155]. 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 [155]. 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.CL] 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 [270]. 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 [270]. If coadministering, use caution and monitor the patient closely.
- 7) Probable Mechanism: inhibition of CYP2C19-mediated metabolism by eslicarbazepine acetate

### 3.5.1.CM] 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 [518], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [519]. The effects of the interaction appear to be estrogen dose-related [520] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [521].
- 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 [509].

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 [510] [511].

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 [512].

**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 [513].

**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 [514].

**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 [515].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [516]. 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 [517].

### 3.5.1.CN] [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 [518], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [519]. The effects of the interaction appear to be estrogen dose-related [520] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [521].

**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 [509].

**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 [510] [511].

**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 [512].

**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 [513].

**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 [514].

**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 [515].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [516]. 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 [517].

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

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

**2)** Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable

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

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

**8)** Literature Reports

**a)** 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 [231].

**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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants (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 effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

**e)** [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 [236].

**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 [237].



g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.CP| Estradiol Valerate

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable

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

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

8) Literature Reports

a) 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 [231].

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 [232]. Some investigators have proposed that the side effects resulted

from enhanced tricyclic antidepressants (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 effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

e) [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 [236].

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 [237].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.CQ| 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 [518], with paradoxical loss of antidepressant effect yet tricyclic toxicity being



manifested simultaneously [519]. The effects of the interaction appear to be estrogen dose-related [520] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [521].

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 [509].

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 [510] [511].

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 [512].

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 [513].

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 [514].

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 [515].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [516]. 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 [517].

### 3.5.1.CR| [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 [518], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [519]. The effects of the interaction appear to be estrogen dose-related [520] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [521].

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

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

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

8) Literature Reports

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

10 patients taking [imipramine](#) alone. However, after two weeks, the five patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received [imipramine](#) 150 mg and [ethinyl estradiol](#) 50 mrg daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [509].

**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 [510] [511].

**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 [512].

**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 [513].

**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 [514].

**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 [515].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [516]. 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 [517].

### 3.5.1.CS] [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 [518], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [519]. The effects of the interaction appear to be estrogen dose-related [520] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [521].

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 [509].

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 [510] [511].

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 [512].

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 [513].

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 [514].

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 [515].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [516]. 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 [517].

### 3.5.1.CT] 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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.CU] **Ethinyl Estradiol**

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable

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

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

8) Literature Reports

a) 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 [231].

**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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants (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 effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

**e)** [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 [236].

**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 [237].



g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.CV] Ethynodiol Diacetate

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable

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

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

8) Literature Reports

a) 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 [231].

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 [232]. Some investigators have proposed that the side effects resulted

from enhanced tricyclic antidepressants (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 effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

e) [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 [236].

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 [237].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.CW] 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 [163]. The effects of [epinephrine](#) may be

potentiated by tricyclic antidepressants [164] 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 [167] [168] [169] [170].

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 [163]. The effects of **epinephrine** may be potentiated by tricyclic antidepressants [164]. 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 [165].

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 [166].

### 3.5.1.CX] **Etonogestrel**

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable

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

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

8) Literature Reports

a) 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 [231].

**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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants (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 effects of oral contraceptives on clomiPRAMINE were 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 [235].

**e)** 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 [236].

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 [237].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.CY] [Fenfluramine](#)

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].



d)) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

e)) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

f)) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.CZ| Fingolimod

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

2)) Summary: Both [clomiPRAMINE](#) and fingolimod may prolong the QT interval and concomitant use should be approached with caution [404] [14]. Initiating fingolimod therapy may decrease heart rate and prolong the QT interval. Drugs that prolong the QT interval, such as [clomiPRAMINE](#), may increase the risk of [torsade de pointes](#) in patients with bradycardia [404]. Monitoring for QT interval prolongation may be warranted if these agents are used concurrently.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution with concomitant administration of [clomiPRAMINE](#) and fingolimod as this may result in additive QT interval prolongation, and may increase the risk of serious cardiovascular effects including [torsade de pointes](#) [404]. If coadministration is required, QT interval monitoring may be warranted.

7)) Probable Mechanism: additive QT interval prolongation

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

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

2)) Summary: Concomitant use of [flecainide](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), should be undertaken with caution due to the potential for additive effects on the QT interval and increased serious cardiac events, including [torsade de pointes](#) [337]. If concomitant therapy is required, closely monitor for QT interval prolongation.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution with the coadministration of [flecainide](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), due to the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects, including [torsade de pointes](#) [337]. If concomitant therapy is required, closely monitor for QT interval prolongation.

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



**3.5.1.DB| Fluconazole**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Due to the potential for additive effects on the QT interval and increased serious cardiac effects, including [torsade de pointes](#), use caution with the coadministration of [fluconazole](#) and other drugs that may prolong the QT interval [339], such as [clomiPRAMINE](#). If concomitant use is required, closely monitor for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised with the concomitant use of [fluconazole](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), as this may result in additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, including [torsade de pointes](#) [339]. If concomitant therapy is required, closely monitor for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.DC| 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 [271]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [272] [278] [279] [280] [281] [282]. 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 [271].
- 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 [271]
- 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 [271].
  - 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 [272].

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 [273].

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 [274].

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) 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. The **desipramine** dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL; 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 [275].

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 with resolution of clinical symptoms [276].

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 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 within five days. The **fluoxetine** dose was increased to 40 mg/day three days later, and the **desipramine** serum level was 419 ng/mL 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 within two weeks [277].

### 3.5.1.DD| **Fluvoxamine**

1) Interaction Effect: **clomiPRAMINE** toxicity (dry mouth, urinary retention, sedation)

2) Summary: Coadministration of **fluvoxamine** and **clomiPRAMINE** was found to significantly increase plasma levels of **clomiPRAMINE** [392]. A bidirectional effect was suggested in which **fluvoxamine** increased **clomiPRAMINE** concentrations (by interfering with N-demethylation) and **clomiPRAMINE** increased **fluvoxamine** levels [393].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

- 6) Clinical Management: Monitor patients for signs of **clomiPRAMINE** and **fluvoxamine** toxicity; lower doses of one or both agents may be required with concomitant therapy.
- 7) Probable Mechanism: decreased **clomiPRAMINE** metabolism
- 8) Literature Reports

a) **Fluvoxamine** has been shown to significantly increase plasma levels of **amitriptyline** and **clomiPRAMINE** and to mildly increase levels of their metabolites **nortriptyline** and **desmethylocloMIPRAMINE**, respectively. This may be due to competitive inhibition of oxidative metabolism in the liver [390].

b) Metabolism of tricyclic antidepressants coadministered with **fluvoxamine** was studied in eight depressed patients (four patients received **clomiPRAMINE**). **Fluvoxamine** was found to interfere with N-demethylation and 8-hydroxylation of **clomiPRAMINE**. The combination of **fluvoxamine** and **clomiPRAMINE** led to increased plasma levels of **clomiPRAMINE** and decreased concentrations of **clomiPRAMINE**'s N-demethylated metabolite, **desmethylocloMIPRAMINE**. In addition, plasma levels of **fluvoxamine** were increased [391].

### 3.5.1.DE] **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 [424]. 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 [424].
- 7) Probable Mechanism: potentiation of cardiovascular effects

### 3.5.1.DF] **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** [158].
- 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**) [158].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated tricyclic agent metabolism

**3.5.1.DG] Fosphenytoin**

- 1) Interaction Effect: an increased risk of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremors)
- 2) Summary: A few case reports have indicated that [imipramine](#) inhibits [phenytoin](#) metabolism resulting in increased serum [phenytoin](#) concentration [109] [110]. Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because [phenytoin](#) is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Consider [phenytoin](#) serum levels if a tricyclic antidepressant is added to therapy or if the patient begins to exhibit signs of toxicity; lower doses of [phenytoin](#) may be required. If [phenytoin](#) is added to tricyclic antidepressant therapy, monitor for clinical efficacy of the tricyclic agent.
- 7) Probable Mechanism: inhibition of [phenytoin](#) metabolism

**3.5.1.DH] 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. [104]. 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 [103]. Therefore, if [serotonin syndrome](#) is suspected, discontinue use of [frovatriptan](#) [104]. Alternatively, if [serotonin syndrome](#) develops, discontinue both offending agents ([frovatriptan](#) and the tricyclic antidepressant) and provide supportive care and other therapy as necessary [103].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [frovatriptan](#) and a tricyclic antidepressant [103], 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](#) [104]. Alternatively, if [serotonin syndrome](#) develops, discontinue both offending agents ([frovatriptan](#) and the tricyclic antidepressant) and provide supportive care and other therapy as necessary [103].
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

**3.5.1.DI] Furazolidone**

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of [clomipramine](#) and an MAOI intended to treat psychiatric disorders is contraindicated. [Clomipramine](#) exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with [clomipramine](#) and an MAOI may result in [serotonin](#)

**syndrome**, a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with **clomiPRAMINE**, and a minimum of 14 days should elapse after discontinuing **clomiPRAMINE** before initiating therapy with an MAOI [156].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of **clomiPRAMINE** and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating **clomiPRAMINE**. Wait at least 14 days after discontinuing **clomiPRAMINE** before initiating therapy with an MAOI [156].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.DJ] **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 [491].

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.DK] **Gemifloxacin**

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

2) Summary: Like other fluoroquinolones, gemifloxacin may prolong the QT interval. Although this interaction has not been evaluated, the concomitant use of gemifloxacin with other drugs that may prolong the QT interval, such as **clomiPRAMINE**, may increase the risk of QT interval prolongation and **torsade de pointes** and should be used together with caution [285]. If coadministration is required, monitoring for QT prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the coadministration of gemifloxacin and other drugs that may prolong the QT interval, such as **clomiPRAMINE**, as coadministration may increase the risk of cardiac adverse events, including **torsade de pointes** [285]. If coadministration is required, monitor for QT prolongation.

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.DL] **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 [504] [505] [506]. 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 [504] [505] [506].

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

### 3.5.1.DM] [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 [504] [505] [506]. 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 [504] [505] [506].

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

### 3.5.1.DN] [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](#) [365] and the risk of QT-interval prolongation [366]. [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 [365]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [366].

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](#) [365] and the risk of QT-interval prolongation [366]. 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 [365]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [366].

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



**3.5.1.DO| 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 [406].
- 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.DP| 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 [138] [139]. 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 [140].
- 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.DQ| 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 [316] [317].
- 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.DR| Haloperidol**

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

2) Summary: QT interval prolongation, [torsade de pointes](#), and sudden death have been reported with [haloperidol](#). Due to the potential for additive effects on the QT interval and risk of [torsade de pointes](#), use caution with the concomitant use of [haloperidol](#) and other medications that may prolong the QT interval [283], such as [clomiPRAMINE](#). If concomitant use is required, close monitoring for QT prolongation is warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when coadministering [clomiPRAMINE](#) and [haloperidol](#) due to an increased risk of QT interval prolongation [283]. If concurrent therapy is required, monitor for QT prolongation.

7) Probable Mechanism: additive effects on QT interval

### 3.5.1.DS] 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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.DT] 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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.DU] [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 [504] [505] [506]. 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 [504] [505] [506].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.DV] [Hydroxychloroquine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: [Hydroxychloroquine](#) has been associated with QT interval prolongation [442] [443], [ventricular premature contractions](#), and [torsade de pointes](#) [443]. 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 [442] [443]. 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.

7J) Probable Mechanism: additive QT interval effects

8J) Literature Reports

aJ) 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 [442].

bJ) 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 [443].

### 3.5.1.DW] Hydroxytryptophan

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

2J) Summary: Serotonergic neurotransmitter systems may be affected by both [clomiPRAMINE](#) [14] and hydroxytryptophan. Concomitant use of [clomiPRAMINE](#) and hydroxytryptophan 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 [clomiPRAMINE](#) and hydroxytryptophan are used concurrently.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [clomiPRAMINE](#) 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.

7J) Probable Mechanism: additive serotonergic effects

### 3.5.1.DX] Ibutilide

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

2J) Summary: QT prolongation and [ventricular arrhythmias](#), including [torsade de pointes](#), have been reported with [ibutilide](#). Although this interaction has not been evaluated, the concomitant use of [ibutilide](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), may increase the risk of QT interval prolongation and [torsade de pointes](#) [292]. If coadministration is required, monitoring for QT prolongation may be warranted.

3J) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ibutilide](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), may result in additive QT interval prolongation and increase the risk of cardiac adverse events, including [torsade de pointes](#) [292]. If coadministration is required, use caution and monitor for QT prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.DY] Iloperidone

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Avoid using [clomiPRAMINE](#) and iloperidone concomitantly due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiovascular events [291].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid using [clomiPRAMINE](#) and iloperidone concomitantly due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiovascular events [291].
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.DZ] Imipramine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [clomiPRAMINE](#) and [imipramine](#) is not common clinical practice. However if using both drugs concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [124] [14].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [clomiPRAMINE](#) and [imipramine](#) is not common clinical practice. However if using both drugs concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [124] [14].
- 7) Probable Mechanism: additive effects on QT interval prolongation

#### 3.5.1.EA] Indacaterol

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Indacaterol doses 2, 4, and 8 times greater than the recommended dosage prolonged the maximum mean corrected QT interval (Fridericia; QTcF) by less than 5 milliseconds in a study of 404 healthy volunteers. Although the QT interval prolongations were not clinically meaningful, extreme caution is recommended when indacaterol is used concomitantly with drugs known to prolong the QT interval, such as tricyclic antidepressants due to the potential increased risk for [ventricular arrhythmias](#) [485].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution when indacaterol is used concomitantly with drugs known to prolong the QT interval such as tricyclic antidepressants due to the potential increased risk for [ventricular arrhythmias](#) [485].
- 7) Probable Mechanism: additive effects on QT interval prolongation

**3.5.1.EB| 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 [395].
- 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 [395].
- 7) Probable Mechanism: inhibition of [norepinephrine](#) transporter function by antidepressants

**3.5.1.EC| Iproniazid**

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. [ClomiPRAMINE](#) exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with [clomiPRAMINE](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with [clomiPRAMINE](#), and a minimum of 14 days should elapse after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [clomiPRAMINE](#). Wait at least 14 days after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].
- 7) Probable Mechanism: additive serotonergic effect

**3.5.1.ED| Isocarboxazid**

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. [ClomiPRAMINE](#) exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with [clomiPRAMINE](#) and an MAOI may result in [serotonin](#)



**syndrome**, a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with **clomiPRAMINE**, and a minimum of 14 days should elapse after discontinuing **clomiPRAMINE** before initiating therapy with an MAOI [156].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of **clomiPRAMINE** and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating **clomiPRAMINE**. Wait at least 14 days after discontinuing **clomiPRAMINE** before initiating therapy with an MAOI [156].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.EE] Ivabradine

1) Interaction Effect: increased risk of QT prolongation

2) Summary: Ivabradine is associated with QT-interval prolongation. Concomitant administration of ivabradine with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval and should be avoided. If concomitant use is required, close cardiac monitoring is necessary [444] [445]. Consider a baseline ECG and on-treatment monitoring.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of ivabradine and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation effects on the QT interval and should be avoided. If concomitant use is required, close cardiac monitoring is necessary [444] [445]. Consider a baseline ECG and on-treatment monitoring.

7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.EF] Ketoconazole

1) Interaction Effect: increased risk for QT prolongation

2) Summary: **Ketoconazole** has been shown to prolong the QT interval [356]. 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 [356]. 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.EG] Lapatinib

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

- 2) Summary: Use caution when using [clomiPRAMINE](#) and lapatinib concomitantly due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiovascular events. If coadministration is required, ECG and [electrolyte monitoring](#) is recommended [290].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [clomiPRAMINE](#) and lapatinib concomitantly due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiovascular events. If coadministration is required, ECG and [electrolyte monitoring](#) is recommended [290].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EH] [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 [504] [505] [506]. 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 [504] [505] [506].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EI] [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 [525]. 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 [525]. If concomitant administration is required, monitor the patient closely.
- 7) Probable Mechanism: potentiation of vascular effects

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

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [clomiPRAMINE](#) and [levofloxacin](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events [289]. If concomitant therapy is required, closely monitor for QT interval prolongation.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [clomiPRAMINE](#) and [levofloxacin](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events [289]. If concomitant therapy is required, closely monitor for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EK] 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 [306].
- 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 [306].
- 7) Probable Mechanism: additive serotonergic effects

### 3.5.1.EL] Levonorgestrel

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes
- 8) Literature Reports

- a) 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 [231].

**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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants (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 effects of oral contraceptives on clomiPRAMINE were 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 [235].

**e)** 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 [236].

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 [237].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.EM] [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 [427]. 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 [427]. 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.EN] [Linezolid](#)

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

2) Summary: Concurrent use of [clomipramine](#) and [linezolid](#), an MAOI, is contraindicated due to the potential for [serotonin syndrome](#). If urgent treatment with [linezolid](#) is necessary in a patient receiving [clomipramine](#) and alternatives are not available, promptly discontinue [clomipramine](#) and administer [linezolid](#) after a risk/benefit evaluation. Monitor for [serotonin syndrome](#) for 14 days or 24 hours after the last dose of [linezolid](#), whichever comes first. [Clomipramine](#) therapy may resume 24 hours after the last dose of [linezolid](#) [156].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [clomipramine](#) and [linezolid](#) (an MAOI) is contraindicated due to the potential for [serotonin syndrome](#). If urgent treatment with [linezolid](#) is necessary in a patient receiving [clomipramine](#) and alternatives are not available, promptly discontinue [clomipramine](#) and administer [linezolid](#) after a risk/benefit evaluation. Monitor for [serotonin syndrome](#) for 14 days

or 24 hours after the last dose of [linezolid](#), whichever comes first. [ClomiPRAMINE](#) therapy may resume 24 hours after the last dose of [linezolid](#) [156]. Monitor for symptoms 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 [103].

7j) Probable Mechanism: additive serotonergic effects

### 3.5.1.EOj Lisdexamfetamine

1j) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2j) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3j) Severity: moderate

4j) Onset: delayed

5j) Substantiation: theoretical

6j) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7j) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8j) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].



e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.EP| [Lopinavir](#)

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

2) Summary: Postmarketing cases of QT interval prolongation and [torsade de pointes](#) have been reported with [lopinavir/ritonavir](#). Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of [lopinavir/ritonavir](#) with other drugs that prolong the QT interval [269], such as [clomiPRAMINE](#). If concurrent therapy is required, monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid the concomitant use of [lopinavir/ritonavir](#) with other drugs that prolong the QT interval, such as [clomiPRAMINE](#), as coadministration may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) [269]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.EQ| [Lorcaserin](#)

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

2) Summary: The concomitant use of [clomiPRAMINE](#), a CYP2D6 substrate [14], and lorcaserin, a CYP2D6 inhibitor, may cause increased [clomiPRAMINE](#) plasma concentrations resulting in increased [clomiPRAMINE](#) adverse effects. Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic neurotransmitter system, such as [clomiPRAMINE](#), may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution [396]. Dose reduction of [clomiPRAMINE](#) may be required when coadministered with lorcaserin, and if lorcaserin therapy is withdrawn, a higher dose of [clomiPRAMINE](#) may be necessary. [ClomiPRAMINE](#) plasma level monitoring may be desirable with coadministration [14].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with the concomitant use of [clomiPRAMINE](#) with lorcaserin as this may cause increased [clomiPRAMINE](#) plasma concentrations and may also result in additive serotonergic effects, increasing the risk of [serotonin syndrome](#) [396]. If concomitant use is required, dose reduction may be warranted for [clomiPRAMINE](#). If lorcaserin therapy is withdrawn, a higher dose of [clomiPRAMINE](#) may be necessary. [ClomiPRAMINE](#) plasma level monitoring may be desirable with coadministration [14].

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

### 3.5.1.ER] **Loxapine**

1J) Interaction Effect: potentiation of impaired cognitive function and motor skills and an increased risk of **respiratory depression**, hypotension, oversedation, and syncope

2J) 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 [215] and use with caution [216].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [215] and use with caution [216].

7J) Probable Mechanism: additive CNS depression

### 3.5.1.ES] **Lumefantrine**

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

2J) Summary: Avoid concomitant use of artemether/lumefantrine and **clomiPRAMINE** due to the additive risk of QT-interval prolongation. Coadministration of artemether/lumefantrine, a CYP2D6 inhibitor, with **clomiPRAMINE**, a CYP2D6 substrate, may significantly increase the plasma concentration of **clomiPRAMINE** and further increase the risk of QT-interval prolongation or other serious adverse effects. If concurrent administration of artemether/lumefantrine and **clomiPRAMINE** is medically required, use caution and monitor the ECG. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [181].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concomitant use of artemether/lumefantrine and **clomiPRAMINE** due to the additive risk of QT-interval prolongation or other serious adverse effects. If concurrent administration of artemether/lumefantrine and **clomiPRAMINE** is medically required, use caution and monitor the ECG. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [181].

7J) Probable Mechanism: additive effects on QT-interval prolongation; inhibition of CYP2D6-mediated metabolism of **clomiPRAMINE**

### 3.5.1.ET] **Mazindol**

1J) Interaction Effect: **hypertension**, other cardiac effects, and CNS stimulation

2J) Summary: Concomitant tricyclic antidepressant (TCA) and **amphetamine** administration has been reported to result in enhanced **amphetamine** effects from the release of **norepinephrine** [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When **amphetamine** analogs are being used to treat **obesity**, it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine

tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.EU] [Medroxyprogesterone Acetate](#)

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

2j) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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].

3j) Severity: minor

4j) Onset: delayed

5j) Substantiation: probable

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

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

8j) Literature Reports

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 [231].

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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant (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 effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

e) [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 [236].

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 [237].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.EV] [Mefloquine](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [clomiPRAMINE](#) and [mefloquine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events [187]. If coadministration is required, monitor for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [clomiPRAMINE](#) and [mefloquine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events [187]. If coadministration is required, monitor for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EW] [Mepenzolate](#)

- 1) Interaction Effect: anticholinergic effects
- 2) Summary: Use caution when coadministering [mepenzolate](#) (an anticholinergic agent) and other anticholinergics as this may result in additive anticholinergic effects, including delayed gastric emptying, increased heartbeat, or [psychosis](#) [157]. If concomitant use is required, monitor patients for adverse effects.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Taking [mepenzolate](#) (an anticholinergic agent) together with other anticholinergics may result in additive anticholinergic effects, including delayed gastric emptying, increased heartbeat, or [psychosis](#) [157]. If coadministration is required, monitor patients for adverse effects.
- 7) Probable Mechanism: additive anticholinergic effects

### 3.5.1.EX] [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 [347]. 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 [103]. 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.EY] [Mephentermine](#)

- 1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical



**6j) Clinical Management:** Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

**7j) Probable Mechanism:** synergistic effects on noradrenergic neurotransmission

**8j) Literature Reports**

**aj) [Amphetamines](#)** may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

**bj) Human pharmacologic studies** have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

**cj) A 55-year-old female patient** was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

**dj) Concomitant administration** of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

**ej) Fifteen patients with DSM-III [major depression](#)**, who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

**fj) There have been claims** based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

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

**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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. These drugs also have additive CNS and respiratory depressant effects.

**3j) Severity:** minor

**4j) 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 [397]. 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.FA] [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](#) [263].

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](#) [263].

7) Probable Mechanism: additive QT-interval prolongation

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

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable

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

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

8) Literature Reports

a) 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 [231].

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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants (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 effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

e) [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 [236].

**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 [237].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (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.FC] [Methadone](#)

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

**2)** Summary: Use caution when administering [clomipramine](#) together with [methadone](#) due to a potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), as both drugs are associated with QT interval prolongation. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval or [dysrhythmias](#) [188].

**3)** Severity: major

**4)** Onset: unspecified

**5)** Substantiation: theoretical

**6)** Clinical Management: Use caution when coadministering [clomipramine](#) and [methadone](#) due to a potential for additive effects on QT interval prolongation and increased risk of [torsade de pointes](#), as both drugs are associated with QT interval prolongation. However, if concurrent therapy is required, monitor cardiovascular status for QT prolongation or [dysrhythmias](#) [188].

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

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

**1)** Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

**2)** Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.FE] [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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.FF] [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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [167] [168] [169] [170].

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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [165].

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 [166].



**3.5.1.FG] Methylene Blue**

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

2J) Summary: Concurrent use of [clomiPRAMINE](#) and methylene blue IV, an MAOI, is contraindicated due to the potential for [serotonin syndrome](#). Reports have involved methylene blue administered intravenously in doses of 1 mg/kg to 8 mg/kg. Reports have not included lower doses or other routes of administration, such as oral or local tissue injection; however, the potential for [serotonin syndrome](#) may exist in these cases. If urgent treatment with methylene blue IV is necessary in a patient receiving [clomiPRAMINE](#) and alternatives are not available, promptly discontinue [clomiPRAMINE](#) and administer methylene blue IV after a risk/benefit evaluation. Monitor for [serotonin syndrome](#) for 14 days or 24 hours after the last dose of methylene blue IV, whichever comes first. [ClomiPRAMINE](#) therapy may resume 24 hours after the last dose of methylene blue IV [156].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [clomiPRAMINE](#) and methylene blue IV (an MAOI) is contraindicated due to the potential for [serotonin syndrome](#). If urgent treatment with methylene blue IV is necessary in a patient receiving [clomiPRAMINE](#) and alternatives are not available, promptly discontinue [clomiPRAMINE](#) and administer methylene blue IV after a risk/benefit evaluation. Monitor for [serotonin syndrome](#) for 14 days or 24 hours after the last dose of methylene blue IV, whichever comes first. [ClomiPRAMINE](#) therapy may resume 24 hours after the last dose of methylene blue [156]. While the risk of concurrent [clomiPRAMINE](#) with other forms of methylene blue is unclear, interactions are possible with methylene blue administered orally, by local injection, or in IV doses lower than 1 mg/kg.

7J) Probable Mechanism: additive serotonergic effects

**3.5.1.FH] Methylphenidate**

1J) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2J) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7J) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8J) Literature Reports

aJ) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as

[desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

**b))** Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

**c))** A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

**d))** Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

**e))** Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

**f))** There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

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

**1))** Interaction Effect: an increased risk of extrapyramidal reactions or [neuroleptic malignant syndrome](#)

**2))** 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 [310]. 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 [311].

**3))** Severity: contraindicated

**4))** Onset: unspecified

**5))** Substantiation: theoretical

**6))** Clinical Management: Concomitant use of tricyclic antidepressant with [metoclopramide](#) is contraindicated [310]. 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 [311].

**7))** Probable Mechanism: unknown

**3.5.1.FJ] Metoprolol**

- 1) Interaction Effect: increased [metoprolol](#) exposure
- 2) Summary: The concomitant use of [metoprolol](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [metoprolol](#), thereby decreasing [metoprolol](#) cardioselectivity [428] [429]. If concomitant administration is required, use with caution, consider [metoprolol](#) dose reduction, and monitor the patient closely.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [metoprolol](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [metoprolol](#), thereby decreasing [metoprolol](#) cardioselectivity [428] [429]. If concomitant administration is required, use with caution, consider [metoprolol](#) dose reduction, and monitor the patient closely.
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [metoprolol](#)

**3.5.1.FK] Metronidazole**

- 1) Interaction Effect: increased risk of QT-interval prolongation and [arrhythmias](#)
- 2) Summary: Concurrent use of [metronidazole](#) with other QT-prolonging drugs was a probable cause of QT-interval prolongation in one study of cardiac ICU patients. Use caution with coadministration of [metronidazole](#) with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs [115].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [metronidazole](#) with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs [115].
- 7) Probable Mechanism: additive QT-interval prolongation
- 8) Literature Reports

a) In a retrospective study, 164 of 501 patients admitted in cardiac ICUs (87.7%) developed QT-interval prolongation potentially linked to inhibition of CYP450-mediated metabolism. Out of 1027 total interactions that were potentially associated with QT-interval prolonging effects, interactions with [metronidazole](#) (n=22) were some of the most common. No patients developed [torsades de pointes](#) during their ICU stays. Close [ECG monitoring](#) at baseline and during concurrent therapy with drugs known to cause QT-interval prolongation is recommended [115].

b) A 71-year-old woman with antibiotic-induced [pseudomembranous colitis](#) developed ECG QTc interval prolongation and [torsades de pointes](#) with concurrent [amiodarone](#) 450 mg bolus followed by 900 mg/day IV and [metronidazole](#) 1500 mg/day oral administration. Baseline QTc interval was 440 msec. [Amiodarone](#) was added after trial fibrillation developed with 3 days of [amiodarone](#) therapy. Conversion to sinus rhythm occurred 2 days later; however, the follow-up ECG revealed a QTc interval of 625 msec. Symptoms progressed to sustained [torsades de pointes](#)-variant [ventricular tachycardia](#) that required emergent [cardioversion/defibrillation](#) to restore normal sinus rhythm. [Amiodarone](#) and [metronidazole](#) were immediately withdrawn, and the QTc

interval slowly returned to baseline values without further clinically significant [arrhythmia](#) events [116].

### 3.5.1.FL] [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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [167] [168] [169] [170].
- 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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [165].

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 [166].

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

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Mifepristone](#) (Korlym(TM)) has been associated with QT interval prolongation. Coadministration of [mifepristone](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), should be avoided due to a risk of additive QT-prolonging effects. Due to the long half-life of [mifepristone](#), at least 2 weeks should elapse between [mifepristone](#) (Korlym(TM)) discontinuation and [clomiPRAMINE](#) initiation. If concurrent therapy is required, use the lowest effective dose; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing the [clomiPRAMINE](#) dose [259]. Monitor closely for prolongation of the QT interval.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6)) Clinical Management: Avoid the concomitant use of [clomiPRAMINE](#) with [mifepristone](#) due to a risk of additive effects on QT interval prolongation. Due to the long half-life of [mifepristone](#), wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before initiating [clomiPRAMINE](#). If concurrent therapy is required, use the lowest effective dose; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing the [clomiPRAMINE](#) dose [259]. Monitor closely for prolongation of the QT interval.

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

### 3.5.1.FN] Mirabegron

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

2)) Summary: Patients concurrently treated with mirabegron, a moderate CYP2D6 inhibitor [527], and [clomiPRAMINE](#), a CYP2D6 substrate [14], may have an increase in [clomiPRAMINE](#) exposure and risk of adverse events. Concomitant use of tricyclic antidepressants with CYP2D6 inhibitors may require lower doses for either the tricyclic antidepressant or the CYP2D6 inhibitor; monitoring of the tricyclic antidepressant is recommended [528].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of mirabegron, a moderate CYP2D6 inhibitor [527], and [clomiPRAMINE](#), a CYP2D6 substrate [14], may result in increased [clomiPRAMINE](#) exposure. Concomitant use of tricyclic antidepressants with CYP2D6 inhibitors may require lower doses for either the tricyclic antidepressant or the CYP2D6 inhibitor; monitoring of the tricyclic antidepressant is recommended [14].

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

### 3.5.1.FO] 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 [173]. 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 [103].

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](#) [173].

7)) Probable Mechanism: additive serotonin effects

8)) Literature Reports

a)) Within a few hours of starting [mirtazapine](#) and shortly after stopping [fluoxetine](#), a 75-year-old woman experienced symptoms consistent with [serotonin syndrome](#). Current medication for depression included [fluoxetine](#), [chlorpromazine](#), and [lorazepam](#). Due to lack of response, [fluoxetine](#) was discontinued and soon afterward [mirtazapine](#) 30 mg/day was started. Within a

few hours of starting [mirtazapine](#), she experience dizziness, headache, nausea, dry mouth, intense anxiety and agitation with suicidal ideas. Other symptoms were difficulty walking, marked resting tremor of the hands, and insomnia. Over the next 3 days, she progressively worsened. [Mirtazapine](#) was discontinued on day 5. Her symptoms improved the following day. [Fluoxetine](#) 20 mg/day was restarted on day 7 with subsequent resolution of dizziness, nausea, headache, and agitation resolution over the following days. Over the next 10 days, tremor, anxiety, difficulty walking, dry mouth, and insomnia improved [174].

b)) A 26-year-old woman with [anorexia nervosa](#) receiving [fluvoxamine](#) for 4 months developed symptoms of [serotonin syndrome](#) after [mirtazapine](#) was initiated. The symptoms of twitching, tremors, agitation, restlessness, and "feeling like she could crawl out of her skin" developed over a period of 4 days after starting [mirtazapine](#) 30 mg/day. Symptoms rapidly progressed to twitching, tremors, and restlessness. She was hospitalized with further symptoms of diaphoresis, flushing, fasciculations, and nausea and treated with [cyproheptadine](#), [acetaminophen](#), and IV fluids. She remained afebrile throughout the event. Symptoms completely resolved within 24 hours [175].

### 3.5.1.FP| Moclobemide

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

2)) Summary: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. [ClomiPRAMINE](#) exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with [clomiPRAMINE](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with [clomiPRAMINE](#), and a minimum of 14 days should elapse after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [clomiPRAMINE](#). Wait at least 14 days after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].

7)) Probable Mechanism: additive serotonergic effect

### 3.5.1.FQ| Modafinil

1)) Interaction Effect: increased plasma levels of [clomiPRAMINE](#) and desmethylclomipramine

2)) Summary: A narcoleptic patient experienced an increase in her [clomiPRAMINE](#) levels when [modafinil](#) was added to her therapeutic regimen. Hepatic enzymes also increased from 2- to 7-fold, requiring that [clomiPRAMINE](#) be discontinued [488]. However, in healthy volunteers, the coadministration of a single dose of [clomiPRAMINE](#) 50 mg during the first day of a 3-day regimen of [modafinil](#) 200 mg daily did not result in an alteration in the pharmacokinetics of either drug [489].

3)) Severity: moderate

4)) Onset: delayed

5)) Substantiation: probable



6) Clinical Management: Monitor patients receiving [modafinil](#) and [clomiPRAMINE](#) concurrently for signs and symptoms of tricyclic intoxication. Liver enzymes should also be closely followed for marked increases.

7) Probable Mechanism: unknown

8) Literature Reports

a) A 60-year-old narcoleptic female was being treated with [clomiPRAMINE](#) without complete resolve of her symptoms. At a [clomiPRAMINE](#) dose of 75 mg under steady-state conditions, her [clomiPRAMINE](#) (CI) and desmethyldclomipramine (DMCI) blood levels were 109 ng/mL and 212 ng/mL, respectively. These levels increased to 129 ng/mL and 208 ng/mL, respectively, when the [clomiPRAMINE](#) dose was increased to 100 mg. When [modafinil](#) 200 mg was instituted, the [clomiPRAMINE](#) dose was decreased to 75 mg, and the CI/DMCI levels increased to 158/238 ng/mL. With [modafinil](#) 400 mg and [clomiPRAMINE](#) 75 mg, the CI/DMCI levels further rose to 210/449 ng/mL. Hepatic enzymes (GOT, GLDH, [GGT](#), GPT) increased from 2- to 7-fold, necessitating the discontinuation of [clomiPRAMINE](#). Three weeks later, the DMCI level was 63 ng/mL, while [clomiPRAMINE](#) was no longer detectable. Hepatic enzymes also returned to baseline. The patient was determined to be a poor metabolizer with regard to cytochrome P450 2D6 (CYP2D6) isoenzymes, indicating that CYP2D6 was not a factor in this drug interaction [487].

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

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

2) Summary: Concomitant use of tricyclic antidepressants, including [clomiPRAMINE](#), and class IA antiarrhythmics, including [morizine](#), may increase the risk of [cardiotoxicity](#) due to similar cardiac effects of these drugs [125] [126]. Therefore, monitoring the patient for signs and symptoms of [cardiac toxicity](#) during coadministration of [clomiPRAMINE](#) and [morizine](#) may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [clomiPRAMINE](#) and [morizine](#) may increase the risk of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs [125] [126]. 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](#) [127].

**3.5.1.FS] Morphine**

- 1) Interaction Effect: increased risk of [paralytic ileus](#)
- 2) Summary: Use caution when coadministering [morphine](#) and an anticholinergic agent as it may result in increased urinary retention or severe constipation, which may lead to [paralytic ileus](#). If concomitant use is required, monitor patients for signs of urinary retention and reductions in gastric motility [286] [287] [288].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [morphine](#) and an anticholinergic agent may result in increased urinary retention or severe constipation, which may lead to [paralytic ileus](#). If concomitant use is required, monitor patients for signs of urinary retention and reductions in gastric motility [286] [287] [288].
- 7) Probable Mechanism: unknown

**3.5.1.FT] Morphine Sulfate Liposome**

- 1) Interaction Effect: increased risk of [paralytic ileus](#)
- 2) Summary: Use caution when coadministering [morphine](#) and an anticholinergic agent as it may result in increased urinary retention or severe constipation, which may lead to [paralytic ileus](#). If concomitant use is required, monitor patients for signs of urinary retention and reductions in gastric motility [286] [287] [288].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [morphine](#) and an anticholinergic agent may result in increased urinary retention or severe constipation, which may lead to [paralytic ileus](#). If concomitant use is required, monitor patients for signs of urinary retention and reductions in gastric motility [286] [287] [288].
- 7) Probable Mechanism: unknown

**3.5.1.FU] Moxifloxacin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: [Moxifloxacin](#) has been associated with QT-interval prolongation. Coadministration with another drug known to prolong the QT-interval should be avoided because of risk for additive effects on the QT-interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). Elderly patients receiving treatment with IV [moxifloxacin](#) may be at an increased risk for QT prolongation. If concurrent use is not avoidable, do not exceed the recommended dose or infusion rate of [moxifloxacin](#) [430] and monitor for changes in the QT-interval.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Moxifloxacin](#) has been associated with QT-interval prolongation. Coadministration with another drug known to prolong the QT-interval should be avoided because of risk for additive effects on the QT-interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). Elderly patients receiving treatment with IV [moxifloxacin](#) may be at an increased risk for QT prolongation. If concurrent use is not avoidable, do not exceed the recommended dose or infusion rate of [moxifloxacin](#) [430] and monitor for changes in the QT-interval.
- 7) Probable Mechanism: additive effects on QT-interval

**3.5.1.FV] 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 [504] [505] [506]. 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 [504] [505] [506].
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.FW] [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](#) [407]. 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](#) [407]. 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.FX] [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 [308].
- 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.FY] [Nilotinib](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Avoid using [clomipramine](#) and nilotinib concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Additionally, nilotinib is

a CYP2D6 inhibitor [184] and **clomiPRAMINE** is a CYP2D6 substrate. Caution is advised when using **clomiPRAMINE** with a CYP2D6 inhibitor as lower doses of **clomiPRAMINE** and/or concomitant drug may be required. If concomitant therapy with **clomiPRAMINE** and nilotinib is required, monitoring of **clomiPRAMINE** levels [14] and for QT interval prolongation [184] is recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid using **clomiPRAMINE** and nilotinib concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [184]. In addition, the coadministration of **clomiPRAMINE** (a CYP2D6 substrate) with a CYP2D6 inhibitor, such as nilotinib, may require lower doses of **clomiPRAMINE** and/or nilotinib. If concomitant therapy with **clomiPRAMINE** and nilotinib is required, monitoring of **clomiPRAMINE** levels [14] and for QT interval prolongation [184] is recommended.

7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.FZ] Norelgestromin

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable

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

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

8) Literature Reports

a) 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 [231].

**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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants (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 effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

**e)** [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 [236].

**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 [237].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (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.GA] 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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [167] [168] [169] [170].
- 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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [165].

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 [166].

### 3.5.1.GB] Norethindrone

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable



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

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

**8j) Literature Reports**

**aj)** 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 [231].

**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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant (TCA) effects secondary to estrogen inhibition of hepatic microsomal enzymes [233].

**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 [234].

**dj)** The effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

e) **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 [236].

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 [237].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.GC] **Norfloxacin**

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

2) Summary: Concomitant use of **norfloxacin** and other QT prolonging drugs, such as **clomiPRAMINE**, may increase the risk of QT interval prolongation and should be undertaken with caution. Geriatric patients may be particularly sensitive to QT prolongation [185]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of **clomiPRAMINE** and **norfloxacin**, both drugs that prolong the QT interval, may increase the potential for serious cardiovascular effects and should be undertaken with caution. Geriatric patients may be particularly sensitive to QT prolongation [185]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GD] **Norgestimate**

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: probable
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes
- 8) Literature Reports

a) 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 [231].

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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant (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 effects of oral contraceptives on [clomipramine](#) were 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 [235].

e) **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 [236].

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 [237].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.GE] **Norgestrel**

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens [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: probable

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

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

8) Literature Reports

a) 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 [231].

**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 [232]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressants (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 effects of oral contraceptives on [clomiPRAMINE](#) were 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 [235].

**e)** [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 [236].

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 [237].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (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.GF] [Nortriptyline](#)

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

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

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Abnormal ECGs and [arrhythmias](#) have been reported with [clomiPRAMINE](#) use [14]. Use caution when using [octreotide](#) with other QT prolonging drugs, such as [clomiPRAMINE](#), due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concurrent therapy is required, monitor ECG for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [clomiPRAMINE](#) and [octreotide](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concurrent therapy is required, monitor ECG for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.GH] [Ofloxacin](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [ofloxacin](#) and [clomiPRAMINE](#) may increase the risk of QT interval prolongation and serious cardiovascular effects and therefore should be undertaken with caution.



Because geriatric patients may be particularly sensitive to QT prolongation associated with drug effects, appropriate precautions should be taken when coadministering these drugs to this patient population [305]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of **clomiPRAMINE** and **ofloxacin** may increase the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects and therefore should be undertaken with caution. Because geriatric patients may be particularly sensitive to QT prolongation associated with drug effects, take appropriate precautions when coadministering these drugs to this patient population [305]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.

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

### 3.5.1.GI] **Olanzapine**

1J) Interaction Effect: an increased risk of seizures

2J) Summary: Psychotropic drugs have been shown to reduce the seizure threshold. A case report describes a patient without an underlying seizure disorder who received treatment with **olanzapine** and **clomiPRAMINE** concomitantly. This combination resulted in seizures which were repeated upon rechallenge with **olanzapine** and **clomiPRAMINE**. It is advised to use caution when administering **olanzapine** concomitantly with **clomiPRAMINE**, or any agent known to reduce seizure threshold [262].

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: It is advised to use caution when administering **olanzapine** concomitantly with **clomiPRAMINE**, or other agents known to lower the seizure threshold.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) A 34-year-old male with **schizophrenia** and **obsessive-compulsive disorder** (OCD) without any underlying seizure disorder, presented for treatment following long-term noncompliance. Inpatient **olanzapine** treatment (20 mg/day) was initiated and positive psychotic symptoms subsequently resolved. Patient was discharged and readmitted because of inability to control symptoms. **ClomiPRAMINE** 250 mg per day was initiated. Within a week, dizziness and myoclonic jerks were reported which quickly progressed to general motor seizures and postictal somnolence (without incontinence). Spike waves and paroxysmal slowing on the EEG was consistent with seizure activity. **ClomiPRAMINE** and **olanzapine** were subsequently withheld, and the seizures were controlled with **diazepam** 30 mg per day for three days. This pattern repeated upon re-challenge with the combination of **olanzapine** and **clomiPRAMINE**. Presumably from the temporal relationship between **clomiPRAMINE** and **olanzapine** administration and seizure manifestation, it can be suspected that this adverse event is due to an interaction between these two drugs. **ClomiPRAMINE** and **olanzapine** are both metabolized by the cytochrome P450 isoenzymes 1A2 and 2D6. One theory is that coadministration may result in elevated levels of both compounds. Although the mechanism by which this interaction occurs is not yet known, it is advised to use caution when administering **olanzapine** concomitantly with **clomiPRAMINE**, or other agents known to lower the seizure threshold [261].

### 3.5.1.GJ] **Olodaterol**

1J) Interaction Effect: an increased risk of cardiovascular adverse events

2) Summary: Olodaterol may produce significant adrenergic-induced cardiovascular effects (eg, increases in pulse rate and blood pressure, and ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression) which may be potentiated by the use of tricyclic antidepressants (TCAs). Use cautiously when olodaterol is administered concurrently with a TCA, especially in patients with preexisting coronary insufficiency, [cardiac arrhythmias](#), [hypertrophic obstructive cardiomyopathy](#), and [hypertension](#) [182]. If coadministration is necessary, monitor the patient closely.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Olodaterol may produce significant adrenergic-induced cardiovascular effects (eg, increases in pulse rate and blood pressure, and ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression) which may be potentiated by the use of tricyclic antidepressants (TCAs). Use cautiously when olodaterol is administered concurrently with a TCA, especially in patients with preexisting coronary insufficiency, [cardiac arrhythmias](#), [hypertrophic obstructive cardiomyopathy](#), and [hypertension](#) [182]. If coadministration is necessary, monitor the patient closely.

7) Probable Mechanism: tricyclic antidepressant potentiation of the adrenergic agonist effects of olodaterol on the cardiovascular system

### 3.5.1.GK] [Ondansetron](#)

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

2) Summary: Use caution when using [clomiPRAMINE](#) and [ondansetron](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events. If concomitant use is required, [ECG monitoring](#) is recommended [186].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when using [clomiPRAMINE](#) and [ondansetron](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events. If concomitant use is required, [ECG monitoring](#) is recommended [186].

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GL] [Oxilofrine](#)

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

2) Summary: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [167] [168] [169] [170].

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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [165].

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 [166].

### 3.5.1.GM] [Oxybutynin](#)

1J) Interaction Effect: decreased [clomiPRAMINE](#) efficacy

2J) Summary: [Oxybutynin](#) was suspected of inducing the metabolism of [clomiPRAMINE](#) in an elderly female patient. Subsequent [dextromethorphan](#) testing of the patient showed that she was an extensive metabolizer (EM) of cytochrome P450 2D6 (CYP2D6). A pilot study exploring the long- and short-term effects of [oxybutynin](#) on the activity of CYP2D6 and another isoenzyme, probably of the CYP3A family, showed that [oxybutynin](#) caused a disproportionate increase of hydroxymorphinan compared with dextromorphan. Because the formation of hydroxymorphinan is mainly dependent on the activity of CYP2D6 and CYP3A4, but only the latter is known to be inducible, the authors suggest that [oxybutynin](#) is an inducer of a CYP3A subfamily [343].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: Patients receiving concurrent therapy with [clomiPRAMINE](#) and [oxybutynin](#) should be monitored for loss of [clomiPRAMINE](#) efficacy, including worsening of symptoms. Plasma levels of [clomiPRAMINE](#) may be helpful in determining if efficacy is being compromised.

7J) Probable Mechanism: induction by [oxybutynin](#) of cytochrome P450 3A-mediated [clomiPRAMINE](#) metabolism

8J) Literature Reports

aJ) A 72-year-old female was receiving [clomiPRAMINE](#) 150 mg daily for depression with a [clomiPRAMINE](#) and desmethylclomipramine blood level of 230 ng/mL and 348 ng/mL, respectively. [ClomiPRAMINE](#) was decreased to 25 mg daily, and [fluvoxamine](#) 100 mg daily was added to therapy. Eighteen days later, her [clomiPRAMINE](#) and desmethylclomipramine levels were 405 ng/mL and 50 ng/mL, respectively. [Oxybutynin](#) 5 mg daily was initiated for [urinary incontinence](#), and within one week the [clomiPRAMINE](#) and desmethylclomipramine levels had decreased to 133 ng/mL and less than 25 ng/mL. They remained low one week later. The patient refused to discontinue [oxybutynin](#) to determine if her [clomiPRAMINE](#) blood levels would again increase [342].

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

1J) 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 [492]. 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 [492]. Dose reductions of one or both agents may be warranted.

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

### 3.5.1.GO| [Paliperidone](#)

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

2) Summary: Avoid using [clomiPRAMINE](#) and [paliperidone](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events [244].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid using [clomiPRAMINE](#) and [paliperidone](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events [244].

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GP| [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](#) [268].

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](#) [268].

7) Probable Mechanism: unknown

### 3.5.1.GQ| [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 [154].

- 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 [154].
- 7) Probable Mechanism: additive QT effects

### 3.5.1.GR] Pargyline

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. [ClomiPRAMINE](#) exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with [clomiPRAMINE](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with [clomiPRAMINE](#), and a minimum of 14 days should elapse after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [clomiPRAMINE](#). Wait at least 14 days after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].
- 7) Probable Mechanism: additive serotonergic effect

### 3.5.1.GS] 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](#) [119]; 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](#) [119]; monitor for signs of additive prolongation of the QT interval during concurrent use.

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

8J) Literature Reports

aJ) Following a single dose of [desipramine](#) 100 mg (a CYP2D6 substrate) added to steady state dosing of [paroxetine](#) 20 mg/day, the [desipramine](#) C<sub>max</sub>, AUC, and t(1/2) increased by a mean of 2-, 5-, and 3-fold [119].

### 3.5.1.GT] Pasireotide

1J) Interaction Effect: increased risk of QT prolongation

2J) Summary: Pasireotide is associated with QT-interval prolongation. In 2 studies, QT prolongation occurred at both therapeutic and supratherapeutic doses of pasireotide. Concomitant administration of pasireotide with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval. ECGs at baseline and at 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents [452].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant administration of pasireotide and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation of the QT interval. ECGs at baseline and 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents [452].

7J) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.GU] Pazopanib

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

2J) Summary: Use caution when using [clomiPRAMINE](#) and pazopanib concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events. If concomitant therapy is warranted, closely monitor ECG and electrolytes ([calcium](#), magnesium, and potassium) [230].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when using [clomiPRAMINE](#) and pazopanib concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events. If concomitant therapy is warranted, closely monitor ECG and electrolytes ([calcium](#), magnesium, and potassium) [230].

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

### 3.5.1.GV] 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 [266]. 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 [267]. 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 [266].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Coadministration of a tricyclic antidepressant metabolized by CYP2D6 and a CYP2D6 inhibitor (ie, peginterferon alfa-2b) may increase the plasma levels of the tricyclic antidepressant and increase the risk for toxicities. Abrupt toxicity may occur when peginterferon alfa-2b is initiated in a patient on stable doses of a tricyclic antidepressant. Lower doses of the tricyclic antidepressant or doses of a CYP2D6 inhibitor (ie, peginterferon alfa-2b) may be required. Additionally, when peginterferon alfa-2b is discontinued, an increased tricyclic antidepressant dose may be required. Monitor levels of tricyclic antidepressants when coadministered with a CYP2D6 inhibitor [266].

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

8) Literature Reports

a) Peginterferon alfa-2b inhibited CYP2D6 activity in a drug interaction study. When healthy subjects were given 50 mg of [desipramine](#) before and after 2 doses of peginterferon alfa-2b 3 mcg/kg, there was a 30% increase in the geometric mean [desipramine](#) AUC (last) compared with administration of [desipramine](#) alone [267].

### 3.5.1.GW] [Pemoline](#)

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as

[desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

**b))** Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

**c))** A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

**d))** Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

**e))** Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

**f))** There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.GX] [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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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

[397]. 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.GY] Perflutren Lipid Microsphere

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Perflutren can prolong the QT interval, and serious cardiopulmonary reactions, including fatalities, have been reported during or after administration of perflutren [135]. Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, use caution if perflutren is administered concomitantly with other drugs that prolong the QT interval, such as [clomiPRAMINE](#). If concomitant therapy is required, monitor closely for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when [clomiPRAMINE](#) and perflutren [135] are administered concomitantly as this may result in additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant therapy is required, monitor closely for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval
- 8) Literature Reports

a) Serious cardiopulmonary reactions, including fatalities, have been reported during or after administration of perflutren-containing microspheres; most serious reactions occurred within 30 minutes of administration. In 221 subjects receiving a perflutren-containing microsphere bolus injection of up to 10 microL/kg, measurement of ECG parameters from 1 hour to 72 hours after administration revealed QTc prolongations of greater than 30 milliseconds in 29% (64/221) of subjects. Among 46 subjects who were further evaluated, 39% experienced associated cardiac rhythm changes. The effects of concomitant drugs on ECG changes has not been studied [135].

### 3.5.1.GZ] [Phendimetrazine](#)

- 1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical

6j) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7j) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8j) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.HA| [Phenelzine](#)

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

2j) Summary: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. [ClomiPRAMINE](#) exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with [clomiPRAMINE](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with

clomiPRAMINE, and a minimum of 14 days should elapse after discontinuing clomiPRAMINE before initiating therapy with an MAOI [156].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of clomiPRAMINE and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating clomiPRAMINE. Wait at least 14 days after discontinuing clomiPRAMINE before initiating therapy with an MAOI [156].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.HB] Phenindione

1J) Interaction Effect: increased risk of bleeding

2J) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants [498] [499]. Considerable interindividual differences may be found [500].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ration) 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.

7J) Probable Mechanism: decreased phenindione metabolism; increased phenindione absorption

8J) Literature Reports

aJ) 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 [495]. This effect was not observed with warfarin.

bJ) 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 [496]. The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

cJ) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs [497]. 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.HC] Phenmetrazine

1J) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2J) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine

tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.HD) [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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.HE] Phenprocoumon

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

**2)) Summary:** Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants [456] [457]. Considerable interindividual differences may be found [458].

**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 [453]. 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 [454]. 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 [455]. 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.HF] [Phentermine](#)

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two

weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [379].

**f)** There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.HG] [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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [167] [168] [169] [170].

**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 [163]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [164]. 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 [165].

**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 [166].

### 3.5.1.HH] [Phenytoin](#)

**1)** Interaction Effect: an increased risk of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremors)

**2)** Summary: A few case reports have indicated that [imipramine](#) inhibits [phenytoin](#) metabolism resulting in increased serum [phenytoin](#) concentration [109] [110]. Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because [phenytoin](#) is

an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Consider [phenytoin](#) serum levels if a tricyclic antidepressant is added to therapy or if the patient begins to exhibit signs of toxicity; lower doses of [phenytoin](#) may be required. If [phenytoin](#) is added to tricyclic antidepressant therapy, monitor for clinical efficacy of the tricyclic agent.

7) Probable Mechanism: inhibition of [phenytoin](#) metabolism

### 3.5.1.HI] [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](#) [348].

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](#) [348].

7) Probable Mechanism: additive QT-interval prolongation

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

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

2) Summary: Concomitant administration of a CYP2C19 substrate (eg, [clomipRAMINE](#)) and a QT-interval prolonging drug (eg, [clomipRAMINE](#)) with piperaquine (a CYP2C19 inhibitor and a QT-interval prolonging drug) is contraindicated because of the increased risk of QT-interval prolongation. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating (based on the half-life) at the time of piperaquine administration, is contraindicated [141].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of a CYP2C19 substrate (eg, [clomipRAMINE](#)) and a QT-interval prolonging drug (eg, [clomipRAMINE](#)) with piperaquine (a CYP2C19 inhibitor and a QT-interval prolonging drug) is contraindicated because of the increased risk of QT-interval prolongation. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating (based on the half-life) at the time of piperaquine administration, is contraindicated [141].

7) Probable Mechanism: inhibition of CYP2C19-mediated metabolism of [clomipRAMINE](#) by piperaquine; additive QT-interval prolongation

### 3.5.1.HK] [Pixantrone](#)

1) Interaction Effect: increased exposure of CYP1A2 substrates

2) Summary: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely [419].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely [419].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism by pixantrone

### 3.5.1.HL] Posaconazole

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use of posaconazole has been associated with QT interval prolongation and torsade de pointes has been reported on rare occasions with posaconazole therapy. Due to the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects, caution is advised when coadministering posaconazole with other drugs that may prolong the QT interval [363], such as clomipramine. If concurrent therapy is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when posaconazole is given concomitantly with other drugs that may prolong the QT interval, such as clomipramine, as this may result in additive effects on the QT interval and an increased risk of serious cardiovascular effects [363]. If concurrent therapy is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.HM] Primidone

- 1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
- 2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.HN] Procainamide

- 1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsades de pointes**, **cardiac arrest**)
- 2) Summary: Concomitant use of tricyclic antidepressants, including **clomiPRAMINE**, and class IA antiarrhythmics, including **procainamide**, may increase the risk of **cardiotoxicity** due to similar cardiac effects of these drugs [125] [126]. Therefore, monitoring the patient for signs and symptoms of **cardiac toxicity** during coadministration of **clomiPRAMINE** and **procainamide** may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of **clomiPRAMINE** and **procainamide** may increase the risk of **cardiotoxicity** (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs [125] [126]. 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** [127].

### 3.5.1.HO] Procarbazine

- 1) Interaction Effect: an increased risk of **serotonin syndrome** (**hypertension**, **hyperthermia**, myoclonus, mental status changes)
- 2) Summary: Concurrent use of **clomiPRAMINE** and an MAOI intended to treat psychiatric disorders is contraindicated. **ClomiPRAMINE** exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with **clomiPRAMINE** and an MAOI may result in **serotonin syndrome**, a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with **clomiPRAMINE**, and a minimum of 14 days should elapse after discontinuing **clomiPRAMINE** before initiating therapy with an MAOI [156].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of **clomiPRAMINE** and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating



**clomiPRAMINE**. Wait at least 14 days after discontinuing **clomiPRAMINE** before initiating therapy with an MAOI [156].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.HPJ **Prochlorperazine**

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

2J) Summary: Abnormal ECG and **arrhythmias** have been infrequently reported with **clomiPRAMINE** [14]. **Prochlorperazine** is a phenothiazine tranquilizer and some drugs in this class have been associated with distortions of the QT interval [260]. If coadministration is required, caution should be used and monitoring for QT interval prolongation may be warranted due to the potential for additive effects on QT prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of **clomiPRAMINE** and **prochlorperazine** may result in additive effects on QT interval prolongation. If coadministration is required, caution should be used and monitoring for QT interval prolongation may be warranted.

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

### 3.5.1.HQJ **Promethazine**

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

2J) Summary: Both **clomiPRAMINE** and **promethazine** may prolong the QT interval. Although this interaction has not been evaluated, the concomitant use of **clomiPRAMINE** with other drugs that may prolong the QT interval, such as **promethazine**, may increase the risk of QT interval prolongation. If coadministration is required, monitoring for QT prolongation may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with the concomitant use of **clomiPRAMINE** and other drugs that may prolong the QT interval, such as **promethazine**, as concurrent use may increase the risk of additive QT interval prolongation. If coadministration is required, monitor for QT interval prolongation.

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

### 3.5.1.HRJ **Propafenone**

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

2J) Summary: Use caution with the concomitant use of **propafenone** with other drugs that have potential to prolong the QT interval, such as **clomiPRAMINE**, due to an increased risk of QT interval prolongation as a result of additive effects from both drugs on the QT interval [284]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with the concomitant use of **propafenone** with other drugs that have potential to prolong the QT interval, such as **clomiPRAMINE**, due to an increased risk of QT interval prolongation as a result of additive effects from both drugs on the QT interval [284]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

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

**3.5.1.HS] 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 [490].
- 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 [490].
- 7) Probable Mechanism: exacerbation of tricyclic antidepressant-induced hypotension by [propranolol](#)

**3.5.1.HT] Propylhexedrine**

- 1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [382] [383]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [384]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [385]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [386]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [372] [373] [374] [375]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [372] [373] [374].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [376].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [377].

d) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation [378] [375].

e) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine [379].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [380]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [381].

### 3.5.1.HU] Protriptyline

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

2) Summary: Concomitant use of clomiPRAMINE and protriptyline is not common clinical practice. However if using clomiPRAMINE and protriptyline concomitantly, use caution due to the potential for additive effects on QT interval prolongation and increased risk of serious cardiovascular effects. Additionally, caution is advised when using protriptyline, a CYP2D6 substrate, with clomiPRAMINE, a CYP2D6 substrate and inhibitor. Monitoring of both protriptyline and clomiPRAMINE levels should be considered [486] [14].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of clomiPRAMINE and protriptyline is not common clinical practice. However if using clomiPRAMINE and protriptyline concomitantly, use caution due to the potential for additive effects on QT interval prolongation and increased risk of serious cardiovascular effects. Additionally, caution is advised when using protriptyline, a CYP2D6 substrate, with clomiPRAMINE, a CYP2D6 substrate and inhibitor. Monitoring of both protriptyline and clomiPRAMINE levels should be considered [486] [14].

7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.HV] Quetiapine

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

2) Summary: The concomitant use of quetiapine with 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, including torsade de pointes [353] [354]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of quetiapine may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with 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, including [torsade de pointes](#) [353] [354]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7) Probable Mechanism: additive effects on QT interval

### 3.5.1.HW] [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 [325], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [326]. The effects of the interaction appear to be estrogen dose-related [327] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [328].

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 [245].

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 [318]. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [319].

c) In one 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 [320].

d) 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 [321].

e) [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 estrogen](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogen](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [250].

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 [322].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [323]. 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 [324].

### 3.5.1.HX] [Quinidine](#)

1) Interaction Effect: increased [clomiPRAMINE](#) plasma concentrations; an increased risk of [cardiotoxicity](#)

2) Summary: Concomitant use of [clomiPRAMINE](#), a CYP2D6 substrate, and [quinidine](#), a CYP2D6 inhibitor, may result in increased [clomiPRAMINE](#) exposure and an increased risk of [clomiPRAMINE](#) adverse effects due to inhibition of [clomiPRAMINE](#) metabolism [14]. Additionally, 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 [125] [126]. Monitoring the patient for

increased [clomiPRAMINE](#) adverse effects during concomitant use and for [clomiPRAMINE](#) 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 [clomiPRAMINE](#) and [quinidine](#) may result in increased [clomiPRAMINE](#) exposure [14]. 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 [125] [126]. Monitor for increased [clomiPRAMINE](#) side effects if [clomiPRAMINE](#) is coadministered with [quinidine](#). Conversely, if [quinidine](#) is discontinued from therapy, monitor for [clomiPRAMINE](#) efficacy. Also monitor the patient for signs and symptoms of [cardiac toxicity](#), including any changes in the ECG.

7) Probable Mechanism: inhibition of CYP2D6-mediated [clomiPRAMINE](#) metabolism by [quinidine](#); additive cardiac effects

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](#) [127].

### 3.5.1.HY] [Quinine](#)

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

2) Summary: Avoid using [clomiPRAMINE](#) and [quinine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [160]. If concomitant therapy is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid using [clomiPRAMINE](#) and [quinine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [160]. If concomitant therapy is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.HZ] [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 [159].

3) Severity: contraindicated



- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of [ranolazine](#) and CYP2D6 substrates, such as tricyclic antidepressants, may increase antidepressant plasma levels. When concurrent use of a tricyclic antidepressant and [ranolazine](#) is required, an antidepressant dose adjustment based on clinical response may be necessary [159].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated tricyclic antidepressant metabolism

#### 3.5.1.IA] [Rasagiline](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. [ClomiPRAMINE](#) exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with [clomiPRAMINE](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with [clomiPRAMINE](#), and a minimum of 14 days should elapse after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [clomiPRAMINE](#). Wait at least 14 days after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].
- 7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.IB] [Ritonavir](#)

- 1) Interaction Effect: increased [clomiPRAMINE](#) serum concentrations
- 2) Summary: The concurrent administration of [clomiPRAMINE](#), a tricyclic antidepressant with metabolism involving CYP2D6 [14], and [ritonavir](#), a CYP2D6 inhibitor, may result in increased [clomiPRAMINE](#) serum levels. If coadministration is necessary, monitoring of [clomiPRAMINE](#) levels is recommended [14], and a decrease in [clomiPRAMINE](#) dose may be necessary [411] [412].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [clomiPRAMINE](#) and [ritonavir](#) as this may lead to increased [clomiPRAMINE](#) serum levels. Increased monitoring and/or a decrease in [clomiPRAMINE](#) dose [clomiPRAMINE](#) may be necessary [14] [411] [412].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [clomiPRAMINE](#) metabolism

#### 3.5.1.IC] 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](#) [369]. SAME was shown to hasten the onset of

therapeutic response of [imipramine](#) in a clinical trial involving 40 patients, without serotonergic side effects [370]. 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 [371].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: S-adenosylmethionine (SAME) 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 SAME and [clomipramine](#) (Iruela et al, 1993). If SAME 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](#) [368].

### 3.5.1.ID] 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 [106]. 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.IE] Saquinavir**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of ritonavir-boosted [saquinavir](#) with other QT prolonging drugs, such as [clomiPRAMINE](#), may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#). These drugs should be used concomitantly only when no alternatives are available and the potential benefits outweigh the potential risks. Do not initiate concomitant therapy in patients with a baseline QT interval of greater than 450 milliseconds. In patients with a baseline QT interval of less than 450 milliseconds, perform an on-treatment ECG approximately 3 to 4 days after therapy is initiated. During concomitant therapy, if a subsequent QT interval reading is greater than 480 milliseconds or has increased by more than 20 milliseconds from baseline, evaluate whether to discontinue either [clomiPRAMINE](#) or ritonavir-boosted [saquinavir](#) or both [161]. Additionally, concurrent administration of [clomiPRAMINE](#) (a CYP2D6 substrate) and [saquinavir](#) boosted with [ritonavir](#) (a CYP2D6 inhibitor) may result in increased [clomiPRAMINE](#) levels and monitoring of [clomiPRAMINE](#) levels is recommended during coadministration [14].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of ritonavir-boosted [saquinavir](#) with other QT interval-prolonging drugs, such as [clomiPRAMINE](#), may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#). These drugs should be used concomitantly only when no alternatives are available and the potential benefits outweigh the potential risks. Do not initiate concomitant therapy in patients with a baseline QT interval of greater than 450 milliseconds. In patients with a baseline QT interval of less than 450 milliseconds, perform an on-treatment ECG approximately 3 to 4 days after therapy is initiated. During concomitant therapy, if a subsequent QT interval reading is greater than 480 milliseconds or has increased by more than 20 milliseconds from baseline, evaluate whether to discontinue either [clomiPRAMINE](#) or ritonavir-boosted [saquinavir](#) or both [161]. Additionally, monitoring of [clomiPRAMINE](#) levels is recommended during coadministration with ritonavir-boosted [saquinavir](#) as [clomiPRAMINE](#) levels may increase [14].
- 7) Probable Mechanism: additive effects on QT interval prolongation

**3.5.1.IF] 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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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.IG| [Selegiline](#)

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

2)) Summary: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. [ClomiPRAMINE](#) exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with [clomiPRAMINE](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with [clomiPRAMINE](#), and a minimum of 14 days should elapse after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [clomiPRAMINE](#). Wait at least 14 days after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].

7)) Probable Mechanism: additive serotonergic effect

### 3.5.1.IH| [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 [441].

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 [441].

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

### 3.5.1.II] [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](#) [344].

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](#) [344].

7J) Probable Mechanism: additive effects on QT interval

### 3.5.1.IJ] [Sodium Phosphate](#)

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

2J) Summary: Use caution when using [clomiPRAMINE](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Prolongation of QT interval associated with [electrolyte imbalances](#) (eg, hypokalemia and [hypocalcemia](#)) and rare but serious reports of [arrhythmias](#) have been noted with [sodium phosphate](#) therapy [162]. If concurrent therapy is required, monitor closely for QT prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when using [clomiPRAMINE](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [162]. If concurrent therapy is required, monitor closely for QT prolongation.

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

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

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

2J) Summary: Use caution when using [clomiPRAMINE](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Prolongation of QT interval associated with [electrolyte imbalances](#) (eg, hypokalemia and [hypocalcemia](#)) and rare but serious reports of [arrhythmias](#) have been noted with [sodium phosphate](#) therapy [162]. If concurrent therapy is required, monitor closely for QT prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when using [clomiPRAMINE](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [162]. If concurrent therapy is required, monitor closely for QT prolongation.

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

**3.5.1.IL] Sodium Phosphate, Monobasic**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [clomiPRAMINE](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Prolongation of QT interval associated with [electrolyte imbalances](#) (eg, hypokalemia and [hypocalcemia](#)) and rare but serious reports of [arrhythmias](#) have been noted with [sodium phosphate](#) therapy [162]. If concurrent therapy is required, monitor closely for QT prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [clomiPRAMINE](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [162]. If concurrent therapy is required, monitor closely for QT prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.IM] Solifenacin**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Postmarketing cases of abnormal ECG and [arrhythmia](#) have been infrequently reported with [clomiPRAMINE](#) [14] and QT interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [solifenacin](#). The concomitant use of [solifenacin](#) with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#) and should be used with caution [297]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [solifenacin](#) with other drugs that may prolong the QT interval may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [297]. If concomitant use is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

**3.5.1.IN] Sorafenib**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [clomiPRAMINE](#) and [sorafenib](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concomitant therapy is required, [monitoring of ECG](#) and electrolytes ([calcium](#), magnesium, and potassium) is recommended [171].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when using [clomiPRAMINE](#) and [sorafenib](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concomitant therapy is required, [monitoring of ECG](#) and electrolytes ([calcium](#), magnesium, and potassium) is recommended [171].
- 7) Probable Mechanism: additive effects on the QT interval



**3.5.1.IO| Sotalol**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: The concomitant use of [sotalol](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), is not recommended due to the potential for additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#) [172]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [sotalol](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), is not recommended due to the potential for additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#) [172]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

**3.5.1.IP| 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](#) [410].
- 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](#) [410].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.IQ| 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 [128] [129], [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 [130], as well as concomitant use of monoamine oxidase inhibitors with tricyclic antidepressants [131] [132] [133]. Coadministration of [amitriptyline](#) and St. John's Wort decreased the area under the concentration-time curve of [amitriptyline](#) and its metabolite [nortriptyline](#) [134]; 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.IR] 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 [501] [502] [503].
- 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 [501] [502] [503].
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

**3.5.1.IS] Sunitinib**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Sunitinib](#) has been associated with prolongation of the QT interval in a dose-dependent manner, with [torsade de pointes](#) occurring in less than 0.1% patients exposed to [sunitinib](#). Due to the potential for additive effects on the QT interval and increased risk for [torsade de pointes](#), caution should be used when [clomiPRAMINE](#) and [sunitinib](#) are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels [176].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the concomitant use of [clomiPRAMINE](#) and [sunitinib](#), as coadministration may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#). If concomitant use is required, consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels [176].
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.IT] 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 [350].
- 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 [350].
- 7) Probable Mechanism: additive serotonergic effect

**3.5.1.IU] Telavancin**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: In clinical trials, prolongation of the QT interval was observed with telavancin use. Therefore, caution is advised if telavancin is used concomitantly with other drugs that may prolong the QT interval [423], such as [clomiPRAMINE](#). If concomitant therapy is required, closely monitor for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on QT interval prolongation, use caution if telavancin is administered concurrently with other drugs that may prolong the QT interval [423], such as [clomiPRAMINE](#). If concomitant therapy is required, closely monitor for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation
- 8) Literature Reports

a) In 3 clinical trials, QTc prolongation greater than 60 msec was observed in 1.5% (15 of 2062) of patients treated with telavancin 10 mg/kg compared with 0.6% (6 of 2062) patients treated with [vancomycin](#). In these studies, 21% (214 of 1029) of telavancin-treated patients and 16% (164 of 1033) of vancomycin-treated patients received concomitant medications known to prolong QTc. Of the patients experiencing QTc prolongation of greater than 60 msec, 9 telavancin-treated patients and 1 vancomycin-treated patient received concomitant medications known to prolong the QTc interval, and less than 1% in each group did not receive a concomitant medication known to prolong the QTc interval. A separate analysis revealed that 1 telavancin-treated patient and 2 vancomycin-treated patients experienced a QTc greater than 500 msec. No patients experienced a cardiac adverse event attributed to QTc prolongation [423].

b) In a randomized, double-blind, multiple-dose, positive- and placebo-controlled, parallel study, maximum QTc prolongation of 11.6 msec (upper 90% confidence limit (CL), 16 msec) and 15.1 msec (upper 90% CL, 20 msec) was observed in patients treated with telavancin 7.5 mg/kg and 15 mg/kg, respectively, compared with 21.6 msec (upper 90% CL 26 msec) in the positive-control group. Healthy subjects (n=160) were randomized to telavancin 7.5 mg/kg, telavancin 15 mg/kg, positive control, or placebo infused over 60 minutes once daily for 3 days. At the end of the infusion, the mean maximum baseline-corrected, placebo-corrected QTc prolongation estimate for telavancin 10 mg/kg (based on interpolation of the data from patients treated with telavancin 7.5 mg/kg and 15 mg/kg) was 12 to 15 msec compared with 22 msec for the positive control. One hour after infusion, the maximum QTc prolongation for telavancin-treated patients was 6 to 9 msec compared with 15 msec for the positive control [423].

**3.5.1.IV] Telithromycin**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: The concomitant use of [telithromycin](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), should be approached with caution due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [304]. If concomitant therapy is required, closely monitor for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: Use caution with the concomitant use of [clomiPRAMINE](#) and [telithromycin](#) due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) [304]. If concomitant therapy is required, closely monitor for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval

### 3.5.1.IW] [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](#) [409].
- 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](#) [409].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.IX] [Tetrabenazine](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of tetrabenazine with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), should be avoided as this may result in additive effects on the QT interval and may increase the risk for serious cardiac events, including [torsade de pointes](#) [177]. If concomitant therapy is required, monitor carefully for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of tetrabenazine with other drugs that prolong the QT interval, such as [clomiPRAMINE](#), as this may result in additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsade de pointes](#) [177]. If concomitant therapy is required, monitor carefully for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.IY] [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 [398] [399] [400]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [401]. 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 [397]. 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| [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](#) [329].
- 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](#) [329].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.JA| [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 [254], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [255]. The effects of the interaction appear to be estrogen dose-related [256] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [257].
- 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 [245].

**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 [246]. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [247].

**c))** A study in which women received [clomiPRAMINE](#) and oral contraceptives or [clomiPRAMINE](#) alone was reviewed [248]. 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.

**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 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 [249].

**e))** [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 estrogen](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogen](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after



taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [250].

**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 [251].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [252]. 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 [253].

### 3.5.1.JB| Toloxatone

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

**2)** Summary: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. [ClomiPRAMINE](#) exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with [clomiPRAMINE](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with [clomiPRAMINE](#), and a minimum of 14 days should elapse after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].

**3)** Severity: contraindicated

**4)** Onset: unspecified

**5)** Substantiation: theoretical

**6)** Clinical Management: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [clomiPRAMINE](#). Wait at least 14 days after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].

**7)** Probable Mechanism: additive serotonergic effect

### 3.5.1.JC| Toremifene

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

**2)** Summary: [Toremifene](#) can prolong the QT interval in a dose- and concentration-dependent manner. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), the concomitant use of [toremifene](#) and other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), should be avoided. If treatment with [clomiPRAMINE](#) is warranted, interrupt [toremifene](#) therapy; however, if coadministration of [clomiPRAMINE](#) with [toremifene](#) cannot be avoided, monitor for QT interval prolongation. Consider [monitoring ECG](#) at baseline and during treatment as indicated in patients at increased risk of QT interval prolongation [465].

**3)** Severity: major

**4)** Onset: unspecified

**5)** Substantiation: theoretical

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

concomitant use is necessary, closely monitor for QT interval prolongation. Consider [monitoring ECG](#) at baseline and during treatment as indicated in patients at increased risk of QT interval prolongation [465].  
7J) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.JD] [Tramadol](#)

1J) Interaction Effect: an increased risk of seizures, [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes), opioid toxicity, and increased concentrations of [tramadol](#) and decreased concentrations of [tramadol](#) active metabolite, M1

2J) Summary: Caution is advised with concomitant use of [clomiPRAMINE](#) and [tramadol](#). [ClomiPRAMINE](#) is a tricyclic antidepressant (TCA) with serotonergic activity and is a CYP2D6 inhibitor. Concomitant use of [tramadol](#) with a 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, such as [clomiPRAMINE](#), 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 TCA or an agent with serotonergic activity is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation and dose increases [484]. Consider monitoring patients for signs and symptoms of opioid toxicity or decreased analgesic effect of [tramadol](#).

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: theoretical

6J) Clinical Management: Caution is advised with concomitant use of [clomiPRAMINE](#) and [tramadol](#). Concomitant use of [tramadol](#) with a tricyclic antidepressant (TCA) or an agent with serotonergic activity, such as [clomiPRAMINE](#), 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 an agent with serotonergic activity is clinically warranted, careful observation is recommended, particularly during treatment initiation and dose increases [484]. Consider monitoring patients for signs and symptoms of opioid toxicity as well as decreased analgesic effect of [tramadol](#).

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

### 3.5.1.JE] [Tranylecypromine](#)

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

2J) Summary: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. [ClomiPRAMINE](#) exerts inhibitory effects on serotonin reuptake. Concurrent administration or overlapping therapy with [clomiPRAMINE](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI before initiating therapy with [clomiPRAMINE](#), and a minimum of 14 days should elapse after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [clomiPRAMINE](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [clomiPRAMINE](#). Wait at least 14 days after discontinuing [clomiPRAMINE](#) before initiating therapy with an MAOI [156].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.JF| [Trazodone](#)

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

2J) Summary: Postmarketing cases of abnormal ECG and [arrhythmia](#) have been infrequently reported with [clomiPRAMINE](#) [14] and QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [367]. Both [clomiPRAMINE](#) and [trazodone](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive effects and the potential for increased risk of [serotonin syndrome](#) [367]. 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 [103]. If coadministration is required, monitoring for QT interval prolongation and signs and symptoms of [serotonin syndrome](#) may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#). Coadministration may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#) [367]. If coadministration is required, appropriate monitoring may be warranted.

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

### 3.5.1.JG| [Trifluoperazine](#)

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

2J) Summary: Use caution when using [clomiPRAMINE](#) and [trifluoperazine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concomitant therapy is required, closely monitor for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Use caution when using [clomiPRAMINE](#) and [trifluoperazine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. If concomitant therapy is required, closely monitor for QT interval prolongation.

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

### 3.5.1.JH| [Trimipramine](#)

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

2)) Summary: Concomitant use of [clomiPRAMINE](#) and [trimipramine](#) is not common clinical practice and may result in additive effects on QT interval prolongation and increased risk of cardiac adverse events. If concomitant use is required, use caution and monitor for QT interval prolongation.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [clomiPRAMINE](#) and [trimipramine](#) is not common clinical practice and may result in additive effects on QT interval prolongation and increased risk of cardiac adverse events. If concomitant use is required, use caution and monitor for QT interval prolongation.

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

### 3.5.1.JI] [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 [504] [505] [506]. 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 [504] [505] [506].

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

### 3.5.1.JJ] [Umeclidinium](#)

1)) Interaction Effect: increased risk of anticholinergic adverse effects

2)) Summary: Avoid coadministration of umeclidinium, an anticholinergic drug, and other drugs that have anticholinergic properties as this interaction may cause increased anticholinergic adverse effects [107].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Avoid concomitant use of umeclidinium, an anticholinergic drug, with other drugs that have anticholinergic properties as this interaction may cause increased anticholinergic adverse effects [107].

7)) Probable Mechanism: additive anticholinergic effects

### 3.5.1.JK] [Valproic Acid](#)

1)) Interaction Effect: an increased risk of [clomiPRAMINE](#) toxicity (agitation, confusion, hallucinations, urinary retention, [tachycardia](#), seizures, coma)

2)) Summary: Comedication with [clomiPRAMINE](#) and [valproic acid](#) may increase serum levels of [clomiPRAMINE](#) resulting in increased side effects. [ClomiPRAMINE](#) toxicity developed in a patient twelve days after [valproic acid](#) therapy was initiated. Metabolism of [clomiPRAMINE](#) is mediated through N-demethylation, hydroxylation, and glucuronidation, and [valproic acid](#) appears to inhibit the enzymes responsible for this mode of metabolism [301].

3)) Severity: moderate

4)) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor serum [clomiPRAMINE](#) levels to avoid overdosing as a result of elevated concentrations of [clomiPRAMINE](#) when comedicated with [valproic acid](#). The [clomiPRAMINE](#) dose may need to be reduced when [valproic acid](#) is added to therapy.

7) Probable Mechanism: inhibition of cytochrome P450 2C-mediated metabolism of [clomiPRAMINE](#)

8) Literature Reports

a) A case report describes a 46-year-old female with personality disorder whose serum [clomiPRAMINE](#) concentrations became elevated after she began concomitant therapy with [valproic acid](#). Antidepressant therapy with [clomiPRAMINE](#) and [lorazepam](#) was initiated while being hospitalized for treatment of her psychiatric disorder. These two agents were chosen to reduce the frequency of panic attacks and to improve symptoms of suicidal and [self-destructive behavior](#). A target dose of [clomiPRAMINE](#) 150 mg/day resulted in serum [clomiPRAMINE](#) levels in the normal range. [Lorazepam](#) was initiated at a dose of 2 mg/day. After two weeks of therapy [valproate](#) was initiated at 1000 mg/day because emotional instability and [self-destructive behavior](#) remained unimproved. After five days of therapy the serum levels of [clomiPRAMINE](#) and desmethylclomipramine increased to 447 ng/mL and 85 ng/mL, respectively. [Valproate](#) serum concentration was 63.2 mcg/mL. The [valproate](#) dose was subsequently adjusted to 1400 mg/day. Seven days after the increase in [valproate](#) dose, [clomiPRAMINE](#) and desmethylclomipramine serum concentrations were 479 ng/mL and 269 ng/mL respectively. Conversely, the [valproate](#) serum level was 55 mcg/mL. The patient noted a feeling of numbness and exaggerated sleep disturbances. After the [clomiPRAMINE](#) dose was reduced to 75 mg/day, these symptoms resolved. The author concludes that the increase in serum [clomiPRAMINE](#) concentrations was primarily due to comedication with [valproate](#) [300].

### 3.5.1.JL] Vandetanib

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

2) Summary: Concomitant use of [clomiPRAMINE](#) and vandetanib, both drugs that may prolong the QT interval, is not recommended due to the potential for additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#). If these drugs must be used concurrently, more frequent [ECG monitoring](#) should be performed. If the corrected QT interval (Fridericia; QTcF) is greater than 500 milliseconds, discontinue therapy until QTcF returns to less than 450 milliseconds and then resume at a reduced dose [178].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [clomiPRAMINE](#) and vandetanib, both drugs that may prolong the QT interval, is not recommended due to the potential for additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#). If these drugs must be used concurrently, more frequent [ECG monitoring](#) should be performed. If the corrected QT interval (Fridericia; QTcF) is greater than 500 milliseconds, discontinue therapy until QTcF returns to less than 450 milliseconds and then resume at a reduced dose [178].

7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.JM] Vardenafil

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

2) Summary: Both [clomiPRAMINE](#) and [vardenafil](#) have been associated with QT interval prolongation [345] [346]. Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), caution is advised when using [vardenafil](#) and drugs that prolong the QT interval,

such as [clomiPRAMINE](#), concomitantly [346]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [clomiPRAMINE](#) and [varденаfil](#) may result in additive effects on the QT interval prolongation and an increased risk of [torsade de pointes](#), and therefore caution is advised [345] [346]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.JN] [Vasopressin](#)

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

2) Summary: Tricyclic antidepressants and [vasopressin](#) have been shown to prolong the QTc interval at the recommended therapeutic dose [431] [432] [433] [434] [435] [436] [437] [438] [439] [440]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.JO] [Vemurafenib](#)

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

2) Summary: Due to a potential increased risk of additive QT interval prolongation and [torsade de pointes](#), the concomitant use of vemurafenib with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), is not recommended [299]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of vemurafenib with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), is not recommended due to an increased risk of serious cardiac adverse events, including [torsade de pointes](#) [299]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.JP] [Venlafaxine](#)

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

2) Summary: Tricyclic antidepressants (TCAs) and [venlafaxine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose [414] [415]. 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 [416]. In addition, [venlafaxine](#) and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [417] [414] [418]. [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 [413].

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 [413].

### 3.5.1.JQ] 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 [402]. 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 [402]. 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.JR] 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](#) [108]. 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 [103]. 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 [108].

3) Severity: major

4) Onset: unspecified

- 5J) Substantiation: theoretical
- 6J) Clinical Management: [Serotonin syndrome](#) has been reported with vilazodone monotherapy and in combination with other serotonergic drugs; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use and monitor for [serotonin syndrome](#). Discontinue use of vilazodone and concomitant serotonergic agents immediately if symptoms of [serotonin syndrome](#) emerge [108].
- 7J) Probable Mechanism: additive serotonergic effects

### 3.5.1.JS| Vinflunine

- 1J) Interaction Effect: increased risk of QT-interval prolongation
- 2J) Summary: Vinflunine is associated with QT-interval prolongation. Concomitant administration of vinflunine with other drugs that prolong the QT interval may have additive prolonging effects on the QT interval and is not recommended [123]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring when vinflunine is coadministered with other QT-prolonging agents.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant administration of vinflunine and QT-prolonging drugs may result in additive QT-interval prolongation effects and is therefore not recommended [123]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.
- 7J) Probable Mechanism: additive QT interval effects

### 3.5.1.JT| Voriconazole

- 1J) Interaction Effect: an increased risk of QT interval prolongation
- 2J) Summary: Postmarketing cases of abnormal ECG and [arrhythmia](#) have been reported with [clomiPRAMINE](#) use [14] and [voriconazole](#) has been associated with QT interval prolongation. As concomitant use of [voriconazole](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), could result in additive effects on QT interval prolongation [303], caution should be used and monitoring for QT interval prolongation may be warranted during coadministration.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of [voriconazole](#) with other drugs that may prolong the QT interval, such as [clomiPRAMINE](#), may result in additive effects on QT interval prolongation [303]. If coadministration is required, caution should be used and monitor for QT interval prolongation.
- 7J) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.JU| Vortioxetine

- 1J) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2J) Summary: Vortioxetine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with caution. [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered

drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy [302].

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 [302].

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.JV] [Warfarin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants [360] [361]. Considerable interindividual differences may be found [362].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: In patients being treated concurrently with [warfarin](#) and [clomiPRAMINE](#), the prothrombin time ratio or [international normalized ratio](#) (INR) should be closely monitored to assess the stability of the anticoagulant response. [Warfarin](#) dosage adjustments may be required.

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 [357]. 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 [358]. 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 [359]. 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.JW] [Yohimbine](#)

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

2) Summary: [Yohimbine increased blood pressure](#) and decreased orthostatic hypotension experienced by depressed patients treated with [clomiPRAMINE](#) on a short-term basis (less than 2 weeks of [clomiPRAMINE](#) treatment, with 4 days of concomitant [yohimbine](#) treatment) [524]. The effect of [yohimbine](#) on orthostatic hypotension induced by [clomiPRAMINE](#) beyond this time frame is unknown. Levels of [yohimbine](#) may continue to increase during the period when [clomiPRAMINE](#) is accumulating (i.e. at the start of therapy and following any dosage changes). Demethylclomipramine may decrease first pass hepatic metabolism of [yohimbine](#), increasing [yohimbine](#) levels and thereby increasing the hypertensive

effect of [yohimbine](#). It was also proposed that patients with depression may have increased sensitivity to the effect of [yohimbine](#) on alpha2-receptors [524].

3J) Severity: moderate

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: Monitor orthostatic and sitting blood pressure in patients taking [clomiPRAMINE](#) who initiate therapy with [yohimbine](#), as [yohimbine](#) may increase blood pressure.

7J) Probable Mechanism: inhibition of hepatic metabolism of [yohimbine](#)

8J) Literature Reports

aJ) [Yohimbine](#) 12 milligrams daily significantly [increased blood pressure](#) in a randomized, double-blind, placebo-controlled, crossover study of 12 patients with depression. Patients had been treated with [clomiPRAMINE](#) 150 mg for a minimum of 48 hours to 1 week maximum and experienced a fall in systolic blood pressure of at least 20 mmHg after 2 and 5 minutes of standing up. Patients received [yohimbine](#) 4 mg three times daily for 3 days, and 4 mg once on day 4. Supine blood pressure was significantly increased on day 1 (p between 0.001 and 0.05) and on day 4 (p between 0.01 and 0.05). Standing blood pressure was significantly increased on day 1 (p between 0.01 and 0.05), and on day 4 (p between 0.001 and 0.05). Hypertensive effects lasted 17 to 24 hours after [yohimbine](#) administration and were accompanied by an increase in heart rate [523].

bJ) Since [yohimbine](#) concentrations are undetectable after 17 to 24 hours, the interaction with [clomiPRAMINE](#) was suggested to involve more than pharmacokinetic alterations. The hypertensive effect of [yohimbine](#) was significantly correlated with plasma [yohimbine](#) levels (p equals 0.0025). Plasma levels of [yohimbine](#) were significantly correlated with plasma levels of demethylclomipramine, the main metabolite of [clomiPRAMINE](#) (p less than 0.006), but not with [clomiPRAMINE](#) levels. The low dose of [yohimbine](#) used in this study had no effect on blood pressure in healthy (non-depressed, normotensive) subjects. Demethylclomipramine may decrease first pass hepatic metabolism of [yohimbine](#), increasing [yohimbine](#) levels and thereby increasing the hypertensive effect of [yohimbine](#). It was proposed that patients with depression may have increased sensitivity to the effect of [yohimbine](#) on alpha2-receptors [523].

### 3.5.1.JX] [Ziprasidone](#)

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

2J) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [421] [422]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [421] [422]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

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

### 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 [534] [535] [536] [537] [538]. 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 [529].

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](#) [530].

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 [531].

d) Individual case reports have documented "blackouts" following modest amounts of alcohol in combination with either [amitriptyline](#) or [imipramine](#) [532], and reversible extrapyramidal effects (parkinsonian effects, [akathisia](#)) with [amoxapine](#) [533].

#### 3.5.2.B] Grapefruit Juice

- 1) Interaction Effect: an increased risk of [clomiPRAMINE](#) toxicity
- 2) Summary: [ClomiPRAMINE](#) is metabolized by several different cytochrome P450 pathways, including CYP1A2, 3A4, and 2D6. Grapefruit juice has been shown to inhibit CYP3A4, causing an increase in the concentrations of drugs which require CYP3A4 for metabolism. Two case reports demonstrated that the addition of grapefruit juice to a [clomiPRAMINE](#) regimen increased the trough plasma concentrations of [clomiPRAMINE](#). Whether the inhibition of [clomiPRAMINE](#) metabolism by grapefruit juice would be sustained over time is not known [540].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor [clomiPRAMINE](#) and desmethylclomipramine trough levels in patients receiving grapefruit juice. Also monitor the patient for signs of [clomiPRAMINE](#) toxicity.
- 7) Probable Mechanism: inhibition of [clomiPRAMINE](#) metabolism by grapefruit juice
- 8) Literature Reports

a) An 8-year-old male patient was being treated with **clomiPRAMINE** 25 mg three times daily for **obsessive-compulsive disorder**. Trough plasma levels of **clomiPRAMINE** (CMI) and desmethyldomipramine (DMCI) were 73 ng/mL and 144 ng/mL, respectively. When 250 mL of grapefruit juice was administered with each dose of **clomiPRAMINE**, the trough levels of CMI and DMCI increased to 198 ng/mL and 233 ng/mL, respectively, after three days. In another case, a 13-year-old female being treated with **clomiPRAMINE** 125 mg daily had a CMI trough blood level of 48 ng/mL and a DMCI trough blood level of 195 ng/mL. Grapefruit juice 250 mL was administered with each **clomiPRAMINE** dose for three days, and the CMI trough level increased to 69 ng/mL while the DMCI trough level decreased to 170 ng/mL [539].

### 3.5.4] Drug-Tobacco Combinations

#### 3.5.4.A] Tobacco

- 1) Interaction Effect: decreased exposure of CYP1A2 substrates
- 2) Summary: Cigarette smoking releases polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism [542] [552], which may reduce CYP1A2 substrate bioavailability. Advise patients to stop smoking during treatment with a CYP1A2 substrate due to the potential reduction in efficacy [541]. If CYP1A2 substrate therapy is required in patients who smoke, consider monitoring for reduced efficacy [542] and adjusting the CYP1A2 substrate dosage if needed [543].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: CYP1A2 substrate bioavailability may be reduced with tobacco smoking. Advise patients to stop smoking during treatment due to the potential reduction in CYP1A2 substrate efficacy [541]. If therapy with a CYP1A2 substrate is required in patients who smoke, consider monitoring for reduced efficacy [542] and adjusting the CYP1A2 substrate dosage if needed [543].
- 7) Probable Mechanism: induction of CYP1A2-mediated metabolism by tobacco smoke
- 8) Literature Reports

a) Smoking 7 to 12 cigarettes/day produced maximum enzyme induction and a significantly lower mean **clozapine** concentration/dose (C/D) ratio in smokers than in nonsmokers (2.8 vs 6 nanograms/mL/mg/day), and similarly with **olanzapine** C/D ratio in another study (6.1 vs 12.8 nanograms/mL/mg/day). Smoking more than 12 cigarettes/day did not produce any further induction nor lower C/D ratio of **clozapine** or **olanzapine** [544].

b) Among patients treated with **mirtazapine** 30 mg/day for 4 weeks, smokers had significantly lower concentrations of S(+)-**mirtazapine** (23 vs 39 nmol/L) and **mirtazapine** S(+)/R(-) ratio (0.28 vs 0.37) than nonsmokers. These effects from smoking remained significant after multivariate analysis [543].

c) In patients receiving stable **clozapine** 100 mg/day, heavy smokers (30 or more cigarettes/day) had a significantly higher mean plasma **clozapine** concentration coefficient of variation (CV) than smokers (30% vs 16%); however, no difference was seen in patients receiving stable **clozapine** 300 or 600 mg/day in a study of patients with **schizophrenia** or **schizoaffective disorder** (N=47) [545].

d) In a study of patients receiving an average **clozapine** dose of 304 mg/day (N=18), **clozapine** and norclozapine (active metabolite) plasma concentrations were significantly lower in smokers (median of 25 cigarettes or 4 pipes/day) compared with nonsmokers. The **clozapine** plasma



concentration in smokers was a significant 3.2-fold lower and norclozapine was 2.3-fold lower compared with plasma concentration in nonsmokers [546].

**e)** Induction of CYP1A2 activity by cigarette smoking significantly reduced [olanzapine](#) plasma concentrations and clinical effectiveness in smokers (10 to 40 cigarettes/day), compared with nonsmokers in a study of adults with thought disorder (N=17). After 15 days of [olanzapine](#) 10 mg/day, the dose-corrected steady-state [olanzapine](#) plasma concentration (C:D) ratio was about 5-fold lower in smokers compared with nonsmokers (1.56 vs 7.9 nanograms/mL/mg). At the same time, Brief Psychiatric Rating Scale total scores were significantly higher for nonsmokers than for smokers (30.4% vs 12.5%) and were positively correlated with the steady-state plasma [olanzapine](#) C:D ratio. Smoking induced a significant 6-fold higher level of CYP1A2 activity in smokers compared with nonsmokers and the index was closely correlated with the steady-state plasma [olanzapine](#) C:D ratio [547].

**f)** Cigarette smoking appears to release polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism. In vivo blood clearance and urine metabolite data from [caffeine](#) demethylation has clearly demonstrated the link between CYP1A2 activity and cigarette smoking, which may have clinical consequences when cigarette smoking occurs with [theophylline](#), [caffeine](#), [tacrine](#), [imipramine](#), [haloperidol](#), [pentazocine](#), [propranolol](#), or [flecainide](#) therapy [542].

**g)** In a study of healthy volunteers (N=14), chronically-exposed passive smokers had a significantly higher mean [theophylline](#) clearance of 60.1 mL/kg/hr compared with 40.9 mL/kg/hr for the nonsmokers. [548]. However, in another study of volunteers (N=5), intense, short-term (5 days) passive smoking did not effect [theophylline](#) disposition [549]. It was concluded that the short duration of exposure to tobacco smoke explained the lack of effect.

**h)** A retrospective study of patients with [schizophrenia](#) (N=50) revealed that cigarette smokers (more than 1 pack/day) had significantly lower plasma concentrations of [haloperidol](#) (16.83 vs 28.8 nanograms/mL) and reduced [haloperidol](#) (active metabolite; 16.76 vs 34.23 nanograms/mL) and significantly increased [haloperidol](#) oral clearance (1.58 vs 1.1 L/min) compared with nonsmokers [550].

**i)** The administration of oral [imipramine](#) 3.5 mg/kg to smokers (15 cigarettes/day) resulted in significantly lower mean plasma levels of combined [imipramine](#) and desmethylinipramine when compared with nonsmokers (160 vs 290 nanograms/mL) [551].

## 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)** [Clomipramine](#) Hydrochloride

**1)** Therapeutic

**a)** Physical Findings

**1) DEPRESSION**

- a)** Improvement in mood, affect, and behavior.
- b)** Improvement in vegetative signs including appetite, sleep pattern, interest in work/recreation, and improvement in weight (if abnormal).

**2) OBSESSIVE COMPULSIVE DISORDER (OCD)**

- a)** Reduction in frequency and severity of obsessions and compulsions characteristic of the patient.
- b)** Improvement in work function, and reduction in amount of time spent with obsessions/compulsions.

**2) Toxic****a) Laboratory Parameters****1) Liver function tests****b) Physical Findings**

- 1)** Signs of central and peripheral hyperactivity: tremor, seizures, manic- like behavior, increased aggression.
- 2)** Constipation, urinary retention, dry mouth, or blurred vision.
- 3)** Orthostatic hypotension, tachycardia.
- 4)** Sexual dysfunction of both genders: impotence, ejaculation problems, anorgasmia.
- 5)** Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in behavior, especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should include at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observation (ie, daily observation) of patients and communication with the prescriber [92].
- 6)** Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms [92].

**4.2] Patient Instructions**

**A) Clomipramine** (By mouth)**Clomipramine**

Treats [obsessive-compulsive disorder](#).

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an [allergic reaction](#) to [clomipramine](#) or similar medicines, or you had a recent [heart attack](#).

How to Use This Medicine:

Capsule, Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

Your doctor may tell you to take the medicine at bedtime to prevent drowsiness during the day.

It is best to take this medicine with food or milk.

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 and an MAO inhibitor (MAOI), such as [linezolid](#) or methylene blue, within 14 days of each other.

Some medicines can affect how [clomipramine](#) works. Tell your doctor if you are using any of the following:

[Buspirone](#), [cimetidine](#), [clonidine](#), [digoxin](#), [fentanyl](#), [guanethidine](#), [haloperidol](#), [lithium](#), [methyphenidate](#), St John's wort, [tramadol](#), tryptophan

A blood thinner (such as [warfarin](#)), depression medicine (such as [fluoxetine](#), [fluvoxamine](#), [paroxetine](#), [sertraline](#)), heart rhythm medicine (such as [flecainide](#), [propafenone](#), [quinidine](#)), triptan medicine for migraine headaches, phenothiazine medicine (such as [chlorpromazine](#), [perphenazine](#), [promethazine](#), [prochlorperazine](#), [thioridazine](#)), seizure medicine (such as [phenobarbital](#), [phenytoin](#)), thyroid medicine

Alcohol, narcotic pain relievers, or sleeping pills may cause you to feel more lightheaded, dizzy, or faint when used with this medicine. Tell your doctor if you drink alcohol or use pain relievers or sleeping pills.

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have [kidney disease](#), liver disease, an [adrenal gland tumor](#) (such as [neuroblastoma](#)), [glaucoma](#), [heart disease](#), depression, mood or mental problems, an [overactive thyroid](#), trouble urinating, or a history of seizures.

This medicine may cause the following problems:

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

Problems with sex (in males)

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

This medicine may make you dizzy or drowsy. Do not drive or do anything that could be dangerous until you know how this medicine affects you.

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

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

Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.

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

Possible Side Effects While Using This Medicine:

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

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

Agitation, confusion, depression, irritability, memory problems

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

Chest pain or a fast, pounding heartbeat

Feeling more excited or energetic than usual, racing thoughts, trouble sleeping

Lightheadedness, dizziness, or fainting

Seizures or tremors

Thoughts of hurting others or yourself, unusual behavior

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

**Cough,** sore throat, runny or stuffy nose

Dry mouth, nausea, vomiting, diarrhea, constipation, loss of appetite, stomach pain or upset

Eye pain, vision changes, seeing halos around lights

Headache

Increased sweating, warmth or redness in your face, neck, arms, or upper chest

Problems with ejaculation or decreased sexual performance

Weight gain or loss

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

#### 4.3] Place In Therapy

**A)** ClomiPRAMINE is indicated for the treatment of **obsessive compulsive disorder**. It is recommended as first-line therapy along with **behavioral therapy** [586]. Other first-line agents include **fluvoxamine**, **fluoxetine**, **sertraline**, and **paroxetine**. However, **clomiPRAMINE** may be selected for patients with concomitant insomnia, **akathisia**, or nausea/diarrhea [587].

**B)** ClomiPRAMINE is not superior to tricyclic antidepressants, including **imipramine** and **amitriptyline**, for treating **major depression**. The drug has been effective for **obsessive compulsive behavior** associated with depression, although **imipramine** seems to be equally suited for treating this disorder. **ClomiPRAMINE** appears to be more effective than **amitriptyline** for relieving chronic pain caused by **trigeminal neuralgia** and tension headaches, but not post-herpetic neuralgia.

**C)** ClomiPRAMINE should be considered for hospital formulary inclusion for the treatment of **obsessive compulsive disorder**, with or without **major depression** [588]. **ClomiPRAMINE** cannot be recommended for first-line treatment of chronic pain induced by **trigeminal neuralgia** or tension headaches until additional controlled studies are conducted, but may be considered for those patients refractory to **amitriptyline**.

#### 4.4] Mechanism of Action / Pharmacology

**A)** Clomipramine Hydrochloride

1) Mechanism of Action

a)] The exact mechanism of action of [clomiPRAMINE](#) is not known. The drug is classified as a tertiary amine tricyclic antidepressant with very potent inhibition of serotonin uptake [582] [583]. The active metabolite, desmethylclomipramine, is a potent [norepinephrine](#) uptake inhibitor and may retain some serotonin uptake inhibition [584] [585].

#### 4.5] Therapeutic Uses

##### 4.5.A] [Clomipramine Hydrochloride](#)

###### 4.5.A.1] [Anorexia nervosa](#)

###### 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:

Found to be no more effective than placebo in producing weight gain in patients with [anorexia nervosa](#)

###### c)] Adult:

1)] In a double-blind, placebo-controlled trial of 16 female [ANOREXIA NERVOSA](#) patients, [clomiPRAMINE](#) 50 milligrams/day was found no more effective than placebo in producing weight gain [1]. Placebo or oral [clomiPRAMINE](#) 50 milligrams was administered once daily to anorexic patients until their predetermined target weight was attained. Patients on [clomiPRAMINE](#) had increased appetite, hunger and calorie consumption during the early part of the study; however, this had no impact on the final outcome. Patients on placebo took a mean of 72 days to attain their target weight, while those on [clomiPRAMINE](#) took a mean of 76 days. Two patients on [clomiPRAMINE](#) and 1 patient on placebo did not complete the study. At a 4-year follow-up, measurement outcomes of nutritional status, sexual adjustment, socioeconomic adjustment and mental state showed no significant differences between the 2 groups [2]. Patients treated with [clomiPRAMINE](#) and placebo- treated patients were at a mean of 94% and 93% of target weight, respectively.

###### 4.5.A.2] [Autistic disorder](#)

###### a)] Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Effective in one study

**c) Adult:**

**1) ClomiPRAMINE** (CMI) was superior to placebo and [desipramine](#) (DMI) on ratings of autistic symptoms such as anger, and compulsive, ritualized behaviors in a 10-week, double-blind crossover comparison of CMI and placebo and CMI and DMI [3].

**4.5.A.3] Cancer pain**

See Drug Consult reference: [MANAGEMENT OF CANCER-RELATED PAIN IN ADULT PATIENTS](#)

**4.5.A.4] Cataplexy - Narcolepsy**

See Drug Consult reference: [NARCOLEPSY AND CATAPLEXY - DRUG THERAPY](#)

**4.5.A.5] Delusional disorder**

**a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Appears effective in the treatment of some types of delusional disorders including DELUSIONAL DISORDER, SOMATIC TYPE and [BODY DYSMORPHIC DISORDER](#)

**c) Adult:**

**1) In a double-blind, cross-over trial clomiPRAMINE** was more effective than [desipramine](#) in patients with [body dysmorphic disorder](#) (BDD) [4]. Patients (n=29) with distress or impairment in functioning due to BDD were randomized to receive first either [clomiPRAMINE](#), a selective serotonin reuptake inhibitor, or [desipramine](#), a selective [norepinephrine](#) reuptake inhibitor (specifically an active placebo), for 8 weeks each. Patients initially received 25 milligrams (mg)/day and were increased to a maximum of 250 mg/day or the highest tolerated dose. Mean dosages attained were 138 mg/day for [clomiPRAMINE](#) and 147 mg/day for [desipramine](#). Assessments were done using a BDD modified version of the Yale-Brown Obsessive-Compulsive Scale (BDD-YBOCS), a modified National Institute of Mental Health Global Obsessive-Compulsive Scale (BDD-NIMH), and the Clinical Global Impression Scale specific to BDD symptoms (BDD-CGI). [ClomiPRAMINE](#) was superior to [desipramine](#) on all 3 of the outcome measures. On the BDD-YBOCS there was a 65% improvement rate with [clomiPRAMINE](#) and a 35% rate with [desipramine](#) (p=0.09). On the BDD-NIMH the response rate was 70% with [clomiPRAMINE](#) and 30% with [desipramine](#) (p=0.02). For the BDD-CGI, [clomiPRAMINE](#) was also significantly better than [desipramine](#) (p=0.01). Also of significance was that patients who were more delusional



appeared to improve more with [clomiPRAMINE](#) therapy (BDD-CGI,  $p=0.007$ ). Adverse effects were similar for both drugs. This is the first study demonstrating the effectiveness of [clomiPRAMINE](#) for BDD.

2)) Four patients with delusional disorder of the somatic type showed clinical improvement with [clomiPRAMINE](#) therapy [5]. All patients persistently complained that something was moving inside their bodies although nothing was found after extensive evaluations. All repeatedly visited physicians complaining of symptoms with 1 patient receiving a possibly unnecessary surgery. Another patient was unresponsive to multiple therapies including sulpiride, nemonapride, mosapramine, levomepromazine, [risperidone](#), [fluphenazine](#), [pimozide](#), and clocapramine. The dosage of [clomiPRAMINE](#) ranged from 60 to 120 milligrams daily and the time to improvement ranged from 27 to 52 days. Further studies including comparisons with [pimozide](#) are needed.

#### 4.5.A.6] Depression

##### a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

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:

Oral and intravenous [clomiPRAMINE](#) have been successfully used to treat [dysthymia](#) and [major depression](#) (Faravelli & Pallanti, 1987)

Intravenous therapy has had no advantage over oral therapy (Faravelli & Pallanti, 1987)

Early improvement in severe depressive symptoms may be achieved by using loading doses of oral or intravenous [clomiPRAMINE](#)

##### c) Adult:

1)) Five days after pulse-therapy with oral or intravenous [clomiPRAMINE](#), symptoms of depression significantly improved in 22 inpatients. Patients were given either an evening infusion of 150 milligrams of [clomiPRAMINE](#) and placebo tablets or 150 milligrams of oral [clomiPRAMINE](#) and an isotonic saline infusion. Twenty-four hours later, this was repeated using 200 milligrams of [clomiPRAMINE](#). Pulse-therapy with oral and intravenous [clomiPRAMINE](#) showed no difference in efficacy or side effects in treating depression. In this double-blind randomized trial results were based on the Hamilton Depression, Raskin, and Beck scales [6].

2)) [ClomiPRAMINE](#) was significantly ( $p$  equals 0.02) more effective than placebo in improving mood in 21 depressed patients with probable [Alzheimer's disease](#). Results were based on the Hamilton Depression scores. [ClomiPRAMINE](#)-treated patients showed a significantly ( $p$  less than 0.01) lower Mini-Mental State score than placebo; no significant drug effects were seen on the Independence measure scores. Patients received 6 weeks of [clomiPRAMINE](#) or placebo in a double-blind crossover design. During the first 6 week period, 9 of 11 [clomiPRAMINE](#)-treated patients experienced a complete remission while the same effect occurred in only 3 of 10 placebo-treated patients. [ClomiPRAMINE](#) was administered at 25 mg for 1 week, 50 mg for week 2, 75 mg for week 3, and 100 mg for weeks 4 to 6 [7].

**d) Pediatric:**

1) A single pulse dose of **clomiPRAMINE** 200 milligrams intravenously was administered in a double-blind, placebo-controlled trial of 16 depressed adolescents, (14-to 18-years-old), demonstrating dramatic and rapid reduction in depressive symptoms at day 6 post-clomiPRAMINE infusion, based upon decreases in Hamilton Depression Rating Scale score ( $p = 0.04$ ) and Clinical Global Impression severity score ( $p = 0.003$ ). The **clomiPRAMINE** effect (88% study response rate) may persist for up to 8 weeks in some patients. The authors suggest that gradually administered **clomiPRAMINE** is less effective than pulse intravenous **clomiPRAMINE** due to the pulse regimen's rapid enhancement of serotonergic transmission [8].

**4.5.A.7] Disorder of ejaculation****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:**

Useful in the treatment of ejaculatory disorders

**c) Adult:**

1) Daily dosing with **clomiPRAMINE** was successful in treating **premature ejaculation** in men who were unresponsive to **clomiPRAMINE** 25 milligrams (mg) on an "as needed" basis. Four men who, in an earlier study, were nonresponders to **clomiPRAMINE** 25 mg "as needed" participated in a 12 week study in which they took **clomiPRAMINE** 0, 10, 20, and 30 mg daily, each dose for 3 weeks. Latencies were significantly longer with the 30-mg per day dose than with the previous 25-mg regimen. Ejaculatory control, sexual arousal, and penile rigidity were not significantly affected by treatment. All subjects reported satisfaction with the treatment. Side-effects were mild and generally transient. Of the 3 men who opted to continue **clomiPRAMINE** treatment, 1 chose 30 mg as needed, and 2 chose 20 mg daily [9].

2) **ClomiPRAMINE** 25 milligrams, as needed, effectively increased ejaculatory latency in men with primary **premature ejaculation**. In a prospective, double-blind, placebo controlled, crossover study, patients with primary **premature ejaculation** ( $n=8$ ), **premature ejaculation** and **erectile dysfunction** ( $n=6$ ), and controls ( $n=8$ ) were randomly given **clomiPRAMINE** for a 3 week period and placebo for 3 a week period. Each was to be used 12 to 24 hours before sexual activity. Patients with ejaculatory latency increased their time to ejaculation from approximately 2 to 8 minutes ( $p=0.035$ ). No significant effects occurred in controls and men with **premature ejaculation** and **erectile dysfunction** [10].

3) **ClomiPRAMINE** (CMI) was useful in the treatment of **PREMATURE EJACULATION** [11]. Twenty patients with **premature ejaculation** were randomly allocated to treatment with **clomiPRAMINE** or placebo in a double-blind study. Mean estimated time to ejaculation after vaginal penetration increased to 6.1 minutes on CMI 25 mg and to 8.4 minutes on CMI 50 mg. These estimated times were significantly different from estimated time to ejaculation while on

placebo. The results suggest that low-dose CMI may be useful in the treatment of [premature ejaculation](#).

4j) Two of 3 cases of RETROGRADE EJACULATION were successfully treated with oral [clomiPRAMINE](#) 25 milligrams twice a day. Two of the 3 patients responded with normal ejaculation within 5 days and subsequent conception, while the third patient only partially improved [12].

#### 4.5.A.8] Migraine; Prophylaxis

See Drug Consult reference: MIGRAINE -- RECOMMENDATIONS FOR PROPHYLAXIS IN ADULTS

#### 4.5.A.9] Obsessive-compulsive disorder

FDA Labeled Indication

##### a) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(10 years and older\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### b) Summary:

[ClomiPRAMINE](#) hydrochloride is indicated for the treatment of obsessions and compulsions associated with [obsessive-compulsive disorder](#) in adults, adolescents, and children age 10 years and older [14]

In a 12-week, randomized, placebo-controlled trial, the addition of [clomiPRAMINE](#) or placebo to [fluoxetine](#) was more effective than the addition of [quetiapine](#) to [fluoxetine](#) in reducing symptoms of [obsessive-compulsive disorder](#) (OCD; DSM-IV TR criteria) in adult patients refractory to [fluoxetine](#) monotherapy (n=54) [15].

##### c) Adult:

##### 1j) Monotherapy

a) The effectiveness of [clomiPRAMINE](#) in the treatment of [obsessive-compulsive disorder](#) (OCD) in adults was demonstrated in 2 placebo-controlled, parallel-group trials. Enrolled patients had moderate-to-severe OCD (DSM-III) symptomatology, with mean baseline Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores from 26 to 28 and mean baseline National Institute of Mental Health Clinical Global Obsessive-Compulsive Scale (NIMH-OC) scores of 10. Following 10 weeks of [clomiPRAMINE](#) treatment (maximum, 250 mg/day), patients experienced a mean reduction of approximately 10 points on the YBOCS; and a reduction of 3.5 units on the NIMH-OC, while no clinical response on either scale occurred in the placebo groups [14].

b) Double-blind, placebo-controlled trials have demonstrated the efficacy of [clomiPRAMINE](#) in relieving some obsessive-compulsive symptoms [16] [17] [18] [19] [20].

In a meta-analysis, it was concluded that the most common treatments for [obsessive-compulsive disorder](#) include [clomiPRAMINE](#), [fluoxetine](#), and exposure-based behavior therapy. Results from 25 appropriate treatment studies from 1975 to 1991 revealed that all three treatments were significantly effective for most of the outcome variables (overall severity, anxiety, depression). Exposure was not significantly effective for reducing depressed mood [21].

c) There was no significant difference in treatment outcome with [clomiPRAMINE](#) between those patients with at least one personality disorder and those with no personality disorders. The effect of [Axis II diagnosis](#) on the outcome of treatment with [clomiPRAMINE](#) was determined in 55 patients with [obsessive-compulsive disorder](#). Patients with paranoid, [schizoid](#), or [schizotypal personality disorders](#) (DSM-III) had significantly higher [obsessive-compulsive disorder](#) severity scores at baseline, and the number of personality disorders was strongly related to baseline severity of obsessive-compulsive symptoms. At the conclusion of this 12-week study, the presence of schizotypal, borderline, and [avoidant personality disorders](#), along with the total number of personality disorders, did predict poorer treatment outcome [22].

d) Using standard [Obsessive-Compulsive Disorder](#) (OCD) assessment tools, it was shown that [clomiPRAMINE](#) was significantly more effective than placebo (38 to 44% response vs 3 to 5% response). Two double-blind studies at 21 centers evaluated the efficacy and safety of up to 300 mg/d of [clomiPRAMINE](#) vs placebo in 520 patients with OCD. TCA-like side effects were reported for [clomiPRAMINE](#). Although uncommon, seizures and elevated aminotransferase values are potentially serious side effects of [clomiPRAMINE](#) [23].

e) Ten patients with DSM-III-R [obsessive-compulsive disorder](#) (OCD) who were being treated chronically with [clomiPRAMINE](#) (mean dose, 270 mg/day), were studied to determine the minimum dose of [clomiPRAMINE](#) needed to maintain therapeutic benefit. Gradual, open dose reduction resulted in a mean dose of 165 mg/day, a reduction of 105 mg/day (approximately 40%). This decrease in dose was accompanied by no significant change in three obsessive-compulsive measures, as determined by the paired t-test. These results suggest that even though patients were not able to discontinue medication completely, they were able to do well at lower doses than those used initially in the treatment of the disorder [24].

## 2) Combination Therapy

a) In a 12-week, randomized, placebo-controlled trial, the addition of [clomiPRAMINE](#) or placebo to [fluoxetine](#) was more effective than the addition of [quetiapine](#) to [fluoxetine](#) in reducing symptoms of [obsessive-compulsive disorder](#) (OCD; DSM-IV TR criteria) in adult patients refractory to [fluoxetine](#) monotherapy (n=54). For study inclusion, all patients had a Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores of at least 16, which was also a decrease of less than 35% from baseline, despite at least 8 weeks of [fluoxetine](#) (maximum dose, 80 mg/day). Enrolled patients were randomized to receive [clomiPRAMINE](#) (n=18; initial dose, 25 mg/day; weekly titration up to 75 mg/day; mean dose, 55 mg/day) plus [fluoxetine](#) (maximum dose, 40 mg/day), [quetiapine](#) (n=18, initial dose, 50 mg/day; weekly titration up to 200 mg/day; mean dose, 142 mg/day) plus [fluoxetine](#) (maximum dose, 40 mg/day), or placebo (n=18) plus [fluoxetine](#) (maximum dose, 80 mg/day). Mean final YBOCS scores and the mean change from baseline at week 12 (primary endpoint; intent-to-treat), were significantly improved for both

[clomiPRAMINE](#) (final score, 18; change from baseline, -6.5; 95% CI, -9 to -3.9) and placebo (final score 18; change from baseline, -6.7; 95% CI, -9.6 to -3.8) compared with [quetiapine](#) (final score, 25; change from baseline, -0.1; 95% CI, -2.9 to 2.7) (p less than 0.001 for both). Withdrawal due to adverse effects occurred in 3 patients treated with [clomiPRAMINE](#) (QT prolongation from patient-specific baseline on ECG) and in 1 patient treated with [quetiapine](#) (syncope associated with orthostatic hypotension) [15].

**d) Pediatric:**

**1)** The effectiveness of [clomiPRAMINE](#) in the treatment of [obsessive-compulsive disorder](#) (OCD) in children and adolescents, age 10 to 17 years old, was demonstrated in a placebo-controlled, parallel-group trial. Enrolled patients had moderate-to-severe OCD (DSM-III) symptomatology, with mean baseline Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores from 26 to 28 and mean baseline National Institute of Mental Health Clinical Global Obsessive-Compulsive Scale (NIMH-OC) scores of 10. Following 8 weeks of [clomiPRAMINE](#) treatment (dosed to a maximum of 3 mg/kg or 200 mg/day), patients experienced a mean reduction of approximately 10 points on the YBOCS; and a reduction of 3.5 units on the NIMH-OC, while no clinical response on either scale occurred in the placebo groups [14].

**2)** Continued [clomiPRAMINE](#) treatment seems necessary for children and adolescents. The need for continued [clomiPRAMINE](#) treatment in children and adolescents with [obsessive-compulsive disorder](#) (OCD) was evaluated in a double-blind [desipramine](#) substitution study. Twenty-six children and adolescents with severe primary OCD receiving long-term [clomiPRAMINE](#) maintenance treatment (mean, 17 months) entered an 8-month study. All patients received [clomiPRAMINE](#) for the first 3 months, then half of the patients continued [clomiPRAMINE](#) and half were given [desipramine](#) for the next 2 months, then all subjects were given [clomiPRAMINE](#) for the last 3 months. Eighty-nine percent of the substituted versus 18% of the non-substituted group relapsed during the 2-month comparison period. However, even subjects who continued uninterrupted [clomiPRAMINE](#) treatment experienced obsessive-compulsive symptoms which varied in severity over time [25].

**3)** In a case series, 7 children and adolescents (age range, 9 to 23 years) with [obsessive-compulsive disorder](#), benefited from combination therapy of [clomiPRAMINE](#) and a selective, serotonin reuptake inhibitor. The combination therapy appeared to augment the effectiveness of monotherapy. [ClomiPRAMINE](#) was used in doses of 25 to 100 mg. The serotonin reuptake inhibitors used included: [fluoxetine](#), [sertraline](#), [paroxetine](#), and [fluvoxamine](#). In 2 cases, once the combination was effective, one of the drugs was successfully discontinued. Two cases of QTc interval prolongation occurred [26].

**4.5.A.10] Obsessive-compulsive disorder, Intravenous therapy**

**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:**

Appears effective in the treatment of [obsessive-compulsive disorder](#) even in some patients refractory to oral [clomiPRAMINE](#)

**c) Adult:**

1) Intravenous [clomiPRAMINE](#) was more effective than placebo in the treatment of [obsessive-compulsive disorder](#) (OCD) in patients refractory to oral [clomiPRAMINE](#). In a double-blind 4-week study, OCD patients refractory to oral [clomiPRAMINE](#) were randomized to receive 1-hour infusions of NS 500 mL containing either [clomiPRAMINE](#) (n=28) or placebo (n=23). [ClomiPRAMINE](#) was titrated over 14 infusions from 25 mg to 250 mg daily. Oral [clomiPRAMINE](#) was started in all patients after the infusions. Patients were evaluated using the Clinical Global Impression (CGI) scale. After the seventh infusion, no patients showed improvement. After infusion 14, 6 (20.7%) [clomiPRAMINE](#) patients were responders on the CGI versus none in the placebo group (p less than 0.02). At 1 week after the infusions, 9 out of 21 (43%) [clomiPRAMINE](#) patients were responders according to the CGI (not all patients were evaluated at this time point). Again there were no responders in the placebo group. At 1 month after the infusion, 9 out of 16 patients were rated as overall intravenous [clomiPRAMINE](#) responders. Further study is needed comparing the intravenous route to the oral route of therapy [27].

2) Intravenous pulse loading of [clomiPRAMINE](#) was beneficial in 6 out of 7 patients with [obsessive-compulsive disorder](#). Patients were randomized to receive either oral loading of [clomiPRAMINE](#) (n=8) or intravenous loading (n=7). The intravenous loading consisted of [clomiPRAMINE](#) 150 mg given intravenously over 90 minutes, followed by [clomiPRAMINE](#) 200 mg intravenously, 24 hours later. [Trimethobenzamide](#) hydrochloride 250 mg was given before each dose to reduce nausea. The oral loading consisted of [clomiPRAMINE](#) 150 mg on day 1 and 200 mg given on day 2. Oral [clomiPRAMINE](#) 150 mg was started in all patients 4.5 days after the second dose and increased by 25 mg every fourth day to 250 mg/day. Using the Yale-Brown scale, 6 out of 7 patients in the intravenous group had responded before the oral dosing was started while only 1 in the oral dose group had responded (p=0.009). After 8 weeks, there was no difference in the 2 groups, both had 4 responders (p=0.38). Pulse intravenous loading may be an effective method for quickly testing patient responsiveness to [clomiPRAMINE](#) therapy [28].

3) A 25-year-old woman with [schizophrenia](#) and ego-dystonic checking and cleaning rituals benefited from intravenous [clomiPRAMINE](#). Her [schizophrenia](#) was stabilized with [perphenazine](#) 8 mg daily. She had failed trials of [fluvoxamine](#) and [fluoxetine](#) for her [obsessive-compulsive disorder](#) (OCD). Further deterioration of her OCD led to hospitalization where a course of intravenous [clomiPRAMINE](#) 75 mg was added to her [perphenazine](#). The infusion was repeated the next day. Five days later her Yale-Brown Obsessive-Compulsive score had dropped from 19 to 4. She was maintained on [clomiPRAMINE](#) 150 mg daily and has had no recurrence of her OCD symptoms over the last 6 months [29].

**d) Pediatric:**

1) A single pulse dose of [clomiPRAMINE](#) 200 mg IV has been administered to depressed adolescents (14-to 18-years-old), demonstrating dramatic and rapid reduction in depressive symptoms at day 6 post-clomiPRAMINE infusion as compared to placebo. The [clomiPRAMINE](#) effect may persist for up to 8 weeks in some patients [8].

2) The use of intravenous [clomiPRAMINE](#) in a 15-year-old female patient with [obsessive-compulsive disorder](#) was reported. After oral treatment with [clomiPRAMINE](#) 200 mg and L-tryptophan 4 g at bedtime for 3 weeks and no response, the patient was started on intravenous



[clomiPRAMINE](#). Doses ranged from 200 to 300 mg in 8 of 14 infusions. Dramatic response was seen, with marked reduction of obsessional thoughts and some reduction of compulsive rituals [30].

#### 4.5.A.11] Pain, chronic

##### 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:

Possibly effective for chronic low back pain in selected patients

##### c) Adult:

1) In an open study, 23 out of 30 patients with chronic low back pain responded to [clomiPRAMINE](#) treatment. [ClomiPRAMINE](#) 25 milligrams (mg) was increased to 150 mg/day intravenously during a 10-day hospital stay. After discharge, [clomiPRAMINE](#) 150 mg/day orally was used for 20 days. Patients with lower initial mean scores on the Minnesota Multiphasic Personality Inventory (MMPI) for [hypochondria](#), depression, and hysteria were more likely to respond to treatment (p less than 0.02, p less than 0.05, p less than 0.02, respectively). These study findings may assist in proper patient selection for beneficial [clomiPRAMINE](#) therapy, however further placebo-controlled studies are recommended [31].

2) In 2 case reports, patients with [schizophrenia](#) and obsessive-compulsive symptoms had their chronic back pain alleviated by [clomiPRAMINE](#) [32]. Doses used ranged from 30 to 75 milligrams. The authors believe that the back pain was related to serotonin dysfunction.

#### 4.5.A.12] [Panic disorder](#)

##### a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### b) Summary:

Reported to be effective in the treatment of panic attacks and [AGORAPHOBIA](#)

##### c) Adult:

1)) Low-dose clomiPRAMINE 60 mg/day was as effective as high-dose clomiPRAMINE 150 mg/day in the treatment of phobias, anxiety, and panic attacks in a multi-center study [33]. In an 8-week study, patients were randomized to clomiPRAMINE 150 milligrams (mg)/day (n=56), clomiPRAMINE 60 mg/day (n=51), or placebo (n=51). Doses were titrated over 2 weeks. At the end of 8 weeks, phobias as evaluated on the Cottraux Scale were significantly improved in both clomiPRAMINE groups as compared to placebo (p=0.002). For anxiety, both clomiPRAMINE groups were significantly better than the placebo group as measured on the anxiety subscale of the Cottraux Anxiety Scale (p=0.002). For panic attacks, the average number of attacks during the previous week was not significantly different in either of the clomiPRAMINE groups or for placebo. However, the number of DSM-III-R symptoms of panic attacks was decreased in both clomiPRAMINE groups but not in the placebo group (p=0.03). There was no difference seen between the 2 clomiPRAMINE therapies in these 3 areas. The author notes that differences may have become evident if a longer treatment period had been used.

2)) In a randomized, placebo-controlled, 10-week study, exercise was found to be effective for the treatment of panic disorder, however, clomiPRAMINE was even more effective. Forty-six patients with panic disorder were assigned to either regular aerobic exercise (running), clomiPRAMINE (increasing doses over three weeks up to 112.5 milligrams/day), or placebo capsules. The dropout rate was 31% for the exercise group, 27% for the placebo group, and 0% for the clomiPRAMINE group. On the Bandelow Panic and Agoraphobia Scale, Observer-Rated, clomiPRAMINE and exercise improved anxiety symptoms more effectively than placebo (p less than 0.001, p less than 0.05, respectively). Improvements in the clomiPRAMINE group were seen as early as 4 weeks while exercise improvements were not seen until the 8th week. Patients receiving clomiPRAMINE or placebo experienced more side effects (dry mouth, sweating, mild tremor, dizziness, tachycardia, nausea, constipation, diarrhea) than those in the exercise group. Additional studies are warranted to investigate exercise in the treatment of anxiety disorders, perhaps in combination with drug treatment [34].

3)) Despite lowering the initial starting dose of clomiPRAMINE to 10 milligrams (mg)/day to maximize compliance, a study involving 58 patients with panic disorder (with or without agoraphobia) resulted in a 45% dropout rate due to adverse reactions occurring mostly during the first two weeks of treatment. Of those completing the study, 84% were markedly or moderately improved. The initial dose was clomiPRAMINE 10 mg at bedtime and increased slowly to 20 mg/day after 4 days, then by 10 mg at 1-to 2-week intervals up to 80 mg after 8 weeks. Patients could receive up to 250 mg daily if the drug was tolerated, with the mean daily dosage being 96.9 mg after 13 weeks of treatment. The primary adverse reactions reported were increased nervousness and agitation [35].

4)) ClomiPRAMINE (10 milligrams (mg) for three days and 20 mg for four days) and fluvoxamine (50 mg/day for seven days) were both effective in decreasing the hypersensitivity to 35% carbon dioxide, supporting the serotonergic effect of these drugs to decrease panic attacks through modification of carbon dioxide sensitivity. Thirty-nine panic disorder patients were enrolled in a double-blind, randomized, placebo-controlled study, where each patient was given the 35% carbon dioxide challenge on days 0, 3, and 7. Patients on clomiPRAMINE and fluvoxamine showed significant reduction in sensitivity over placebo after seven days as seen by the percent change on a visual analogue for anxiety scale (p=0.027) [36].

5)) Clinical improvement was modest on agoraphobia in panic disorder patients who failed to respond to exposure-based behavioral treatment and were treated then with clomiPRAMINE (CMI) [37]. Eighteen patients with panic disorder with agoraphobia who had not responded

to previous inpatient [behavioral treatment](#) entered a 12-week, placebo- controlled, double-blind crossover study of [clomiPRAMINE](#) at maximum doses of 150 milligrams/kilogram for 3 weeks. Patient outcome was assessed on measures of phobic avoidance, agoraphobic cognitions, panic, state and trait anxiety, subjective anxiety, and depression. Seventeen of 18 patients completed the study. One patient (placebo group) dropped out after 6 weeks after developing acute gastric pain. On most outcome measures, patients had significantly lower symptom scores at posttest in the active drug period than at posttest in the placebo period. However, while this study showed short-term efficacy of [clomiPRAMINE](#) for agoraphobic patients who did not respond to [behavioral treatment](#), its ability to produce lasting benefits remains to be proven.

6)) [ClomiPRAMINE](#) in low doses (25 to 75 milligrams daily) was reported effective in the treatment of panic ANXIETY and [agoraphobia](#) in outpatients in an uncontrolled 8-week clinical trial [38]. Of 17 patients treated, panic attacks were abolished completely in 13, and markedly decreased in 4 others. In 7 agoraphobic patients, avoidance behavior disappeared in 5. Overall mean doses were 45 milligrams daily, with 8 patients (6 panic and 2 agoraphobic) receiving 25 milligrams daily or less (mean, 18.76 milligrams). There was a trend towards the need for higher doses in [agoraphobia](#) (mean, 56 milligrams) as opposed to [panic disorder](#) (mean, 40 milligrams). Well-controlled clinical trials are required to confirm these findings and determine the optimal dose of [clomiPRAMINE](#) in [panic disorder](#) and [agoraphobia](#).

7)) Oral [clomiPRAMINE](#) was significantly superior to placebo on measures of DEPRESSION, [DYSPHORIA](#), and on several indexes of PHOBIC SYMPTOMS in an 8-week double-blind, placebo-controlled study of 94 agoraphobic women as diagnosed by DSM-III guidelines [39]. [ClomiPRAMINE](#) was started at 25 milligrams/day which was slowly increased up to a maximum of 300 milligrams/day as tolerated. At the end of the study the mean daily dose of [clomiPRAMINE](#) was 83 milligrams. Adverse effects associated with [clomiPRAMINE](#) use included dry mouth, high energy levels, constipation, and increased sweating.

#### 4.5.A.13] [Pervasive developmental disorder](#)

##### a)) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### b)) Summary:

May be effective in adults with [pervasive developmental disorders](#) (PDDs)

##### c)) Adult:

1)) [ClomiPRAMINE](#) was found to be effective in 18 of 35 adult patients (55%) with [pervasive developmental disorders](#) (PDDs) (18 patients with [autistic disorder](#), 6 with [Asperger's disorder](#), 11 with [PDD](#) not otherwise specified). In an open-label study, [clomiPRAMINE](#) was started at 50 milligrams (mg) at bedtime and increased by 50 mg every 3 or 4 days to a maximum dosage of 250 mg daily within 3 weeks and continued for a minimum of 9 additional weeks. Based on the Clinical Global Impression scale, 18 patients were "much" or "very much" improved (p less than 0.001). In

those 18 patients, [clomiPRAMINE](#) significantly reduced total repetitive thoughts and behavior (p less than 0.001), aggression (p less than 0.001), and some aspects of social relatedness such as eye contact and verbal responsiveness (p less than 0.001). Improvements were not related to a specific subtype of [PDD](#). Three patients had seizures during treatment (two having a prior seizure history), prompting the authors to recommend a selective serotonin uptake inhibitor in these patients [40].

#### 4.5.A.14] [Premenstrual syndrome](#)

##### 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 reducing the symptoms of [Premenstrual Syndrome](#) in small studies

##### c) Adult:

1) Intermittent administration of low-dose [clomiPRAMINE](#) (25 to 75 milligrams/day) during the luteal phase only for the treatment of [premenstrual syndrome](#) was effective (N=29), and the onset of clinical effect was shorter than when [clomiPRAMINE](#) was used to treat depression, [panic disorder](#), or [obsessive-compulsive disorder](#) (Sunblad et al, 1993).

2) [ClomiPRAMINE](#) (CMI) was effective in reducing symptoms of [Premenstrual Syndrome](#) (PMS) in a placebo-controlled trial. Forty non-depressed women with severe premenstrual irritability and/or [dysphoria](#) and fulfilling DSM-III-R diagnostic criteria for late luteal phase dysphoric disorder were treated daily for 3 menstrual cycles with either CMI (25 to 75 milligrams/d) or placebo. Both groups had 20 patients. The response rate in the placebo group was 40% compared with 80% for the CMI group. The possible role of serotonin in the pathophysiology of PMS is discussed [41].

3) Subjects reported a dramatic reduction in premenstrual complaints with [clomiPRAMINE](#) therapy. [ClomiPRAMINE](#) was administered orally as 25 to 50 milligrams/day for 5 consecutive menstrual cycles to 5 non-depressed women with severe premenstrual irritability and sadness [42].

#### 4.5.A.15] [Self-injurious behavior](#)

##### a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b)) Summary:**

Useful in certain types of self-injurious behaviors such as severe NAIL BITING

**c)) Adult:**

1)) In an open clinical trial, **clomiPRAMINE** was useful for chronic stereotypic and self-injurious behaviors in 11 consecutive patients with concomitant development disorders [43]. Patients received **clomiPRAMINE** in a mean dosage of 70 milligrams/d (range 25 to 125 mg/d). Ten patients (91%) had marked decreases in rates of target behaviors as early as 2 days after starting treatment and as late as 1 month. No seizures occurred despite the inclusion of six patients with previous histories of epileptic events, and improvement was evident regardless of level of **mental retardation**. These findings support the use of serotonergic medications in this population and the need for further research.

2)) **ClomiPRAMINE** has been helpful in reducing **SELF-MUTILATING BEHAVIOR** in a 25-year-old female patient with **obsessive-compulsive disorder**. Excessive nail-biting and arm-burning with cigarettes was successfully curtailed after 4 months of treatment with CMI at doses of 250 milligrams per day [44].

3)) **ClomiPRAMINE** (CMI) was significantly more effective than **DESIPRAMINE** (DMI) in decreasing severe nail-biting in 25 adult subjects with severe morbid **ONYCHOPHAGIA**. During a 10-week double-blind, crossover trial CMI at 120 milligrams/day was superior to DMI at 135 mg/d as determined by nail-biting rating scale assessments. It is hypothesized that similar biological systems mediate a spectrum of "grooming" behaviors, including onychophagia, **trichotillomania**, and **obsessive-compulsive disorder** [25].

**4.5.A.16] Steinert myotonic dystrophy syndrome****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:**

Has improved some symptoms associated with **myotonic dystrophy**

**c)) Adult:**

1)) **ClomiPRAMINE** (CMI) has improved grip myotonia in patients with **myotonic dystrophy** in a placebo-controlled double-blind, crossover study. Fifteen of 17 patients completed the two 33-day treatment periods separated by a 30-day washout period. Grip myotonia was determined by a standardized test and was video-taped for later analysis. Results showed that mean relaxation time after **clomiPRAMINE** was significantly shorter than after placebo [13].

**4.5.A.17] Trichotillomania****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:**

Effective for short-term treatment of [trichotillomania](#)

**c) Adult:**

1) In a 9-week study comparing [cognitive-behavioral therapy](#) (CBT), [clomiPRAMINE](#), and placebo in the treatment of [trichotillomania](#), CBT significantly reduced symptoms from pretreatment to posttreatment, whereas [clomiPRAMINE](#) and placebo did not. Twenty-three patients were randomized to receive either CBT, [clomiPRAMINE](#) (50 mg at bedtime titrated as tolerated to 250 mg at bedtime), or placebo and were evaluated on a weekly basis by either a psychiatrist ([clomiPRAMINE](#) and placebo patients) or a behavioral psychologist (CBT patients). Of the 16 patients that completed the trial, severity and impairment of [trichotillomania](#) were significantly reduced ( $p=0.002$  and  $p=0.006$ , respectively) in the CBT group ( $n=5$ ); however, significant differences were not noted in the [clomiPRAMINE](#) ( $n=6$ ) or the placebo ( $n=5$ ) groups. [ClomiPRAMINE](#) did produce more changes in pretreatment and posttreatment evaluations ( $p=0.061$ ) than placebo; however, given the low power of the study conventional levels of significance were not achieved. Documented side effects of moderate or severe intensity included tremor, sedation, dry mouth, constipation, memory difficulty, and nausea (Ninan, 2000).

2) Four consecutive patients treated for [trichotillomania](#) (hair-pulling) with [clomiPRAMINE](#) reported initial dramatic reductions in symptoms. However, three of the four patients had relapsed completely at 3-month follow-up, although all four were taking previously effective dosages of the drug. The fourth patient relapsed for about 2 weeks but regained initial treatment benefits. Daily dosage used was 150 milligrams (1), 100 milligrams (2), and 50 milligrams (1) [45].

#### **4.6] Comparative Efficacy / Evaluation With Other Therapies**

##### **4.6.A] [Albuterol](#)**

###### **4.6.A.1] Depression**

a) In depression, [albuterol](#) 6 milligram/day was superior to [clomiPRAMINE](#) 150 milligram/day, both given by intravenous infusion. Ten patients received each drug; symptoms were evaluated by 2 blind observers at days 0, 5, and 15, using the Hamilton rating scale. With [albuterol](#), global improvement on day 5 was significantly superior to [clomiPRAMINE](#). This improvement included mood retardation, anxiety, and insomnia. On day 15, the improvement in the [albuterol](#) group was only slightly increased over the [clomiPRAMINE](#) group. Eight of 10 patients in the [albuterol](#) group, and 5 of 10 patients in the [clomiPRAMINE](#) group demonstrated a clear improvement. An additional 2 patients responded to [clomiPRAMINE](#) 1 week later [609].

##### **4.6.B] [Amineptine](#)**



#### 4.6.B.1] Depression

a) Amineptine and **clomiPRAMINE** were found to have similar antidepressant activity in 62 depressed patients during a 6-week, randomized, double-blind study [591]. Patients were diagnosed with psychotic, non-psychotic, or **melancholic depression** by the investigators; however, the diagnostic criteria were not described. The Hamilton Rating Scale for Depression was used to evaluate therapeutic effects. Oral daily doses of amineptine 100 to 300 milligrams (mean 180 mg) or **clomiPRAMINE** 50 to 150 milligrams (mean 84 mg) were administered during the trial. Improvement in depression symptoms were seen in both groups and no apparent differences in antidepressant activity could be determined. Fifteen patients did not complete the study: 4 on amineptine and 11 on **clomiPRAMINE**.

#### 4.6.C] Amitriptyline

##### 4.6.C.1] Obsessive-compulsive disorder

a) Oral **clomiPRAMINE** produced a statistically significant reduction in the number or severity of obsessive-compulsive symptoms over **amitriptyline** on the Psychiatric Questionnaire for **Obsessive-Compulsive Disorder** [621]. Twenty patients with chronic **obsessive-compulsive disorder** were randomized to receive either **clomiPRAMINE** or **amitriptyline** in a 4-week, double-blind study. Both drugs were started at 75 milligrams/day and increased up to 300 mg/day as tolerated. The **clomiPRAMINE**-treated group demonstrated improvement over **amitriptyline** on depression and anxiety scales. The most common adverse effects experienced by both groups included dizziness, drowsiness, and dry mouth. Three patients failed to complete the study: 1 from each group due to syncope and 1 from **amitriptyline** due to an inadequate response.

##### 4.6.C.2] Pain, chronic

a) **ClomiPRAMINE** appeared to be better than **amitriptyline** in treating chronic **trigeminal neuralgia** and **tension headache** pain; however, **amitriptyline** was more effective in treating **postherpetic neuralgia** during a 3-month, randomized, single-blind study with 67 chronic pain sufferers [622]. Oral **clomiPRAMINE** was dosed between 20 and 75 milligrams daily in 3 divided doses, while oral **amitriptyline** was dosed between 30 and 110 milligrams daily in 3 divided doses. Severe sedation was the most commonly reported adverse effect with **amitriptyline**. The most severe adverse effect with **clomiPRAMINE** was motor agitation, which was experienced by 4 of 35 (10%) patients. Anticholinergic effects were experienced with both drugs.

#### 4.6.D] Buspirone

##### 4.6.D.1] Obsessive-compulsive disorder

a) A double-blind study comparing **busPIRone** and **clomipramine** in the treatment of **obsessive-compulsive disorder** (OCD) was performed [638]. Eighteen of 20 study entrants completed the trial, which included an initial 2-week placebo washout period, a 2-week titration phase (in which doses were increased as tolerated to a daily maximum of 60 mg **busPIRone** or 250 mg **clomipramine**), and a 4-week dose maintenance phase; subjects then received half the maximum tolerated dose for 4 days, followed by 3-1/2 weeks of placebo. Although the study was conducted in a crossover fashion, with the alternate treatment given after the 3-1/2 week placebo washout, the trial results were analyzed as a parallel design because subjects did not return to baseline status by the beginning of the second active treatment period. The authors reported similar efficacy of the 2 active treatments, with at least half of the patients in each group evidencing a minimum of 20% improvement in several measures of OCD and one of depression. However, the small sample size may have obscured differences in efficacy. The authors noted that response was not correlated with dose

of [clomipramine](#) (mean 225 +/- 49 mg/day) or of [busPIRone](#) (mean 58 +/- 7 mg/day), or with previous use of benzodiazepines. [BusPIRone](#) warrants further study as a possible treatment for OCD.

#### 4.6.E] [Citalopram](#)

##### 4.6.E.1] Depression

a) [ClomiPRAMINE](#) (a tricyclic antidepressant with potent 5-HT reuptake inhibiting properties) 150 milligrams once daily was statistically superior to [citalopram](#) 40 milligrams once daily in the treatment of endogenously depressed patients in a 5-week double-blind study (n=75). [ClomiPRAMINE](#) appeared to have a faster onset and was particularly more effective in improving sleep disturbances, although other depressive symptoms were also improved to a greater degree with this agent compared to [citalopram](#). In the subgroup of patients with nonendogenous depression in this study (n=27), a similar trend was observed in favor of [clomiPRAMINE](#); however, the number of patients treated was too small to enable an effective comparison. Orthostatic symptoms, dry mouth, and perspiration were seen only with [clomiPRAMINE](#), whereas nausea, vomiting, and headache were more common with [citalopram](#) [655]. Flaws in this study were that fixed doses of each agent were employed and the duration of 5 weeks may have been too short. The onset of full antidepressant effects of [citalopram](#) may take 5 to 6 weeks. Titrating the dose of each agent based on clinical response would enable a more effective comparison in that optimal doses for specific patients could be achieved. A further comparison of these agents with flexible dosing regimens is warranted.

##### 4.6.E.2] Efficacy

a) A small, 5-week, double-blind study reported significant orthostatic hypotensive effects (systolic pressure) in depressed patients treated with [clomiPRAMINE](#) 150 milligrams once daily but not [citalopram](#) 40 milligrams once daily. Diastolic blood pressure was also significantly reduced, although to a lesser extent, with [clomiPRAMINE](#), whereas this change did not occur in citalopram-treated patients [656].

b) Similar findings were reported in a clinical efficacy comparison of [clomiPRAMINE](#) and [citalopram](#) [655], and these results are consistent with other clinical data suggesting the lower propensity of [citalopram](#) to induce cardiovascular effects compared to tricyclic antidepressants [657].

#### 4.6.F] [Desipramine](#)

##### 4.6.F.1] [Autistic disorder](#)

a) [ClomiPRAMINE](#) was superior to both [desipramine](#) and placebo for treatment of autistic behavior such as stereotypies, anger, and compulsive, ritualized behavior. [ClomiPRAMINE](#) and [desipramine](#) were both superior to placebo, and had equivalent effects in reducing hyperactivity of patients with [autistic disorder](#) [593].

##### 4.6.F.2] [Diabetic neuropathy](#)

a) [ClomiPRAMINE](#) and [desipramine](#) both significantly reduced symptoms of [diabetic neuropathy](#) as determined by investigators and self-rating compared to placebo [594]. In this double-blind, placebo-controlled, 3-way crossover study, 19 patients were randomized to 2 weeks of treatment with oral [desipramine](#) 50 or 200 milligrams/day, [clomiPRAMINE](#) 50 or 75 milligrams/day, or placebo. Washout between treatment periods was not mentioned. Both agents significantly reduced [neuropathy](#) symptoms (pain, paresthesia, dysesthesia, numbness, nightly deterioration, and sleep disturbances) compared to placebo. No significant difference between active treatments was observed. The most common adverse

events, which occurred with equal frequency in each active treatment group, included dry mouth, sweating, orthostatic dizziness, and fatigue.

#### 4.6.F.3] Nail biting

a) ClomiPRAMINE was superior to desipramine in the treatment of onychophagia in a 10-week, double-blind, crossover study. Of the 25 patients enrolled, only 14 completed the study perhaps due to lack of other psychiatric disturbance [597].

#### 4.6.F.4] Obsessive-compulsive disorder

a) ClomiPRAMINE was significantly more effective than desipramine for treating obsessive compulsive disorder. In a 10-week, double-blind, crossover study forty-eight children and adolescents (ages 6 to 18 years) received clomiPRAMINE (mean dose 150 milligrams/day) then desipramine (153 milligrams/day). Sixty-four percent of the patients who received clomiPRAMINE for the first time demonstrated a relapse during desipramine therapy. None of the subjects studied exhibited a greater than 20% improvement as measured by the Global OCD Scale during a 2-week, single-blind trial before receiving active treatment. Unlike desipramine, clomiPRAMINE decreased obsessive compulsive ratings and depression ratings measured on the Hamilton and NIMH Depression scales [595].

b) Oral clomiPRAMINE was superior to desipramine in a comparative, crossover, double-blind study in childhood obsessive-compulsive disorder [595]. Twenty-one adolescents were treated for 5 weeks with each drug in increasing doses to a maximum of 3 mg/kg. The results showed a striking superiority of clomiPRAMINE over desipramine and the clinical effects were not attributed to a nonspecific antidepressant effect. In a group of 26 obsessive compulsive patients on clomiPRAMINE who entered a double-blind drug substitution study using desipramine, clomiPRAMINE was superior to desipramine [596].

#### 4.6.F.5] Paraphilia

a) ClomiPRAMINE and desipramine had similar efficacy in the treatment of paraphilias in a small, double-blind, crossover study. Eight of 15 patients completed the study in which each patient received a mean maximal daily dose of clomiPRAMINE 162.5 milligrams (range 75 to 250 mg) and desipramine 212.5 milligrams (range 100 to 250 mg) for 5 weeks after a 2-week placebo phase. Four of the 8 were also clinically depressed, and there was a great deal of variety in the paraphilias demonstrated by this patient population. As measured by the Schedule for Affective Disorders and Schizophrenia, Lifetime Version, severity of paraphilic symptoms were significantly decreased by both clomiPRAMINE ( $p$  less than or = 0.005) and desipramine ( $p$  less than or = 0.002) as compared with placebo [598].

#### 4.6.F.6] Trichotillomania

a) ClomiPRAMINE was superior to desipramine in the treatment of trichotillomania (hair pulling) during a 10-week, double-blind, crossover study involving 13 women [599]. In this study, capsules containing 50 mg of either clomiPRAMINE or desipramine were administered; initial doses were 50 milligrams daily, increasing over 3 weeks to a maximum dose of 3 milligrams/kilogram/day (250 mg daily). Mean maximal doses were 180 mg daily for clomiPRAMINE and 173 mg daily for desipramine. ClomiPRAMINE was superior to desipramine by a physician's rating scale and a trichotillomania-impairment scale. Symptom severity was reduced more with clomiPRAMINE as compared to desipramine and clomiPRAMINE patients were better able to resist the urge to pull hair as opposed to desipramine patients. ClomiPRAMINE appears to be a specific antitrichotillomanic agent; this disorder may be related to an obsessive-compulsive disorder.

#### 4.6.G] Diazepam

##### 4.6.G.1] Agoraphobia

a) ClomiPRAMINE was significantly superior to diazepam in the treatment of 33 agoraphobic patients during a 12-week, multicentered, randomized, double-blind study [600]. The patients were diagnosed with agoraphobia or social phobia of at least a 1-month duration. Both drugs were administered orally in low doses initially; the doses were then increased to 25 to 150 milligrams in 3 divided daily doses for clomiPRAMINE and to 10 to 30 milligrams in 3 divided daily doses of diazepam. Headaches were experienced more in the diazepam group, while dry mouth and drowsiness were more prevalent in the clomiPRAMINE group. By the end of the study, clomiPRAMINE demonstrated significant improvement over diazepam in total scores for situational anxiety, interference in life-style, and accompanied travel distance on an agoraphobia inventory.

#### 4.6.H] Dixyrazine

##### 4.6.H.1] Panic disorder

a) Dixyrazine plus clomiPRAMINE was more effective than clomiPRAMINE alone in reducing the number of panic attacks. In a 12-week study, 45 patients with panic attacks (with or without agoraphobia) were treated with clomiPRAMINE titrated up to 250 milligrams (mg) per day plus either dixyrazine 50 mg per day or placebo. Patients treated with dixyrazine plus clomiPRAMINE showed a larger reduction in the Hamilton Anxiety Rating Scale (HARS-P) scores for panic attacks from week 6 to week 12 than the patients in the placebo group (p less than 0.05). The reduction of the number of panic attacks and the increase in patients daily functioning were also significantly greater in the dixyrazine- clomiPRAMINE group (p less than 0.05) [625].

#### 4.6.I] Dothiepin

##### 4.6.I.1] Depression

a) Although dothiepin and clomiPRAMINE were equally capable of diminishing depressive symptoms in a randomized, double-blind, parallel-group comparison of the two tricyclic antidepressants over 6 weeks, adverse events affected 50% more patients in the clomiPRAMINE group (n=45) than in the dothiepin group (n=47), and overall more than one-quarter of patients in the clomiPRAMINE group withdrew because of such adverse effects as dry mouth, dizziness, and somnolence [602].

#### 4.6.J] Doxepin

##### 4.6.J.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 [589].

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. [590].

#### 4.6.K] Fluoxetine

##### 4.6.K.1] Obsessive-compulsive disorder

a) Treatment with fluoxetine (FLX) was compared with treatment with clomiPRAMINE (CMI) in two groups of patients with obsessive compulsive disorder (OCD) using two different experimental designs. In the first group of 11 patients with OCD studied using a randomized, double-blind, crossover design, treatment with FLX (20 to 80 milligrams/d) for 10 weeks was found to produce therapeutic effects similar to that obtained with CMI (50 to 250 milligrams/d) for 10 weeks. There were significantly fewer total side effects reported during FLX than CMI treatment. Drug tapering and placebo substitution in the 4-week crossover interval phase led to substantial relapses in OCD symptoms and depression. In addition, response to the second drug took as long as response to the first drug, despite a putative common mechanism of action of serotonin uptake inhibition. A second group of 21 patients with OCD that had been previously stabilized on CMI with at least partial benefit were crossed over to FLX in double blind fashion. After 10 weeks of FLX, most patients manifested behavioral rating scores of OCD and depressive symptoms that were comparable with pre-crossover ratings completed during CMI treatment. A significant exacerbation in OCD and depression ratings as well as a similar lag in therapeutic efficacy were also noted in this second cohort of patients with OCD. Platelet serotonin concentrations were reduced 95% during both CMI and FLX treatment periods. These results suggest that FLX may represent a viable alternative to CMI in the treatment of OCD, although more studies with larger sample sizes are needed [603].

b) ClomiPRAMINE (CMI) and fluoxetine (FLX) were shown to be equally effective in the treatment of 120 patients with DSM-III major unipolar depressive disorder over a 6-week period. Adverse effects were more frequent with CMI. Those that did occur with FLX tended to disappear during the course of the study [604].

#### 4.6.L] Fluvoxamine

##### 4.6.L.1] Anxiety

a) Fluvoxamine and clomiPRAMINE were comparable in reducing anxiety symptoms in patients with agoraphobia with panic attacks (APA), generalized anxiety disorders (GAD), and obsessive-compulsive disorders (OCD) as classified by DSM-III during a randomized, double-blind study [610]. Of the 50 patients in this study, 39 diagnosed with APA, 5 with GAD, and 6 with OCD. Patients were randomly assigned to receive either clomiPRAMINE, up to 150 milligrams/day, or fluvoxamine, up to 100 milligrams/day, for the 6-week study. Both drugs demonstrated significant improvement in anxiety symptoms after drug therapy when compared to pretreatment.

##### 4.6.L.2] Cataplexy

a) Both fluvoxamine and clomiPRAMINE improved cataplexy, but not narcolepsy, in 18 patients with these diseases during a cross-over study [611]. It was not revealed if either the patients or researchers were blinded to drug therapy. It should be noted that 15 of the 18 patients were receiving clomiPRAMINE 25 to 100 milligrams/daily at the start of the trial, and may have been accustomed to the adverse effects of clomiPRAMINE. Also, if the patients were not blinded to drug therapy, some patients may have associated more adverse effects with a new drug, fluvoxamine. Patients were randomly allocated to receive fluvoxamine or clomiPRAMINE for a 3-week interval. After a 1-week drug-free period, the patients crossed over to the other drug. The daily dosing range for both drugs ranged from 25 to 200 milligrams/day. All patients were clinically assessed by observers on 5 occasions. The observers' impression was that fluvoxamine caused a moderate reduction in the frequency of attacks of cataplexy and sleep paralysis in



most subjects. [Fluvoxamine](#) abolished [cataplexy](#) in 4 patients and [sleep paralysis](#) in 2 patients; only 12 of the 18 patients completed the fluvoxamine-treatment period. The observers felt that [clomiPRAMINE](#) was more effective than [fluvoxamine](#) in preventing both [cataplexy](#) and [sleep paralysis](#). [ClomiPRAMINE](#) abolished [cataplexy](#) in 4 patients and [sleep paralysis](#) in 5 patients.

#### 4.6.L.3] Depression

a) SUMMARY: Several double-blind, short-term studies have demonstrated [fluvoxamine](#) to be as effective as [clomiPRAMINE](#) in the treatment of depression [612] [613]. Anticholinergic adverse effects appear to be less common with [fluvoxamine](#) therapy.

b) [Fluvoxamine](#) and [clomiPRAMINE](#) were compared for antidepressant activity in a 6-week, randomized, double-blind study of 43 outpatients with [major depression](#) [612]. Oral [fluvoxamine](#) 100 to 300 milligrams or oral [clomiPRAMINE](#) 50 to 150 milligrams was administered once daily in the evening. Assessments of the HAM-D (Hamilton Rating Scale for Depression) during the study and at the end failed to demonstrate any significant differences in antidepressant activity between the 2 drugs. The incidence of anticholinergic adverse effects were slightly more significant in the [clomiPRAMINE](#)-treated group.

c) [ClomiPRAMINE](#) and [fluvoxamine](#) appeared to be equally effective in the treatment of depression for 36 female inpatients during a 4-week, randomized, double-blind study [613]. Patients were randomized to receive either oral [clomiPRAMINE](#) or oral [fluvoxamine](#) 50 milligrams 3 times daily. [Diazepam](#) 10 to 30 mg/day for severe agitation and/or anxiety was the only other psychotropic agent administered. Significant improvements in the Hamilton Rating Scale for Depression, the Clinical Global Impression, and the [Zung Self-Rating Depression scale](#) were seen in both treatment groups. Anticholinergic adverse effects appeared more frequently in the [clomiPRAMINE](#)-treated patients, while gastrointestinal effects were more prevalent in the [fluvoxamine](#) group.

d) [Fluvoxamine](#) and [clomiPRAMINE](#) appeared to have similar clinical efficacy in the treatment of [endogenous depression](#) for 30 unipolar and bipolar inpatients during a 4-week, randomized, double-blind study [612]. Both drugs were administered orally in doses of 150 to 300 milligrams/day in 3 divided doses. At the end of the study, the fluvoxamine-treated patients demonstrated a 73% improvement on the Hamilton Rating Scale for Depression, while the [clomiPRAMINE](#)-treated patients had a 62% improvement. In the bipolar patients, 3 of 4 on [fluvoxamine](#) responded, while only 1 of 5 on [clomiPRAMINE](#) demonstrated a good response on the CGI Global Change Scale. Overall, the differences in efficacy between the 2 drugs were not statistically significant. Adverse anticholinergic effects were significantly more prevalent in the [clomiPRAMINE](#)-treated group.

e) Both [clomiPRAMINE](#) and [fluvoxamine](#) produced significant improvements on the Hamilton Rating Scale for Depression (HAM-D) in 32 patients with mixed depression during a 4-week, randomized, double-blind study [614]. The average daily dosage was 130 milligrams and 132.8 milligrams for [fluvoxamine](#) and [clomiPRAMINE](#), respectively. The mean percentage improvement on the HAM-D for the fluvoxamine-treated patients was 63.8%, and for the [clomiPRAMINE](#)-treated patients it was 66.3%.

#### 4.6.L.4] Obsessive-compulsive disorder

a) [Fluvoxamine](#) (150 to 125 milligrams/day) and [clomiPRAMINE](#) (100 to 250 milligrams/day) were equally effective in the treatment (10 weeks) of 66 outpatients with [obsessive compulsive disorder](#). Both treatments were well-tolerated. [Fluvoxamine](#) produced fewer anticholinergic adverse effects and caused less sexual dysfunction than [clomiPRAMINE](#), but caused more headache and insomnia [615]. under [OBSESSIVE COMPULSIVE DISORDER](#) add:

b) In a randomized, double-blind study of 26 patients with [obsessive compulsive disorder](#) without comorbid diseases, [fluvoxamine](#) and [clomiPRAMINE](#), each titrated from an initial dose of 50 milligrams (mg) in the evening up to a maximum of 300 mg daily within two weeks, were equally effective (38% improvement over baseline with [fluvoxamine](#) versus 40% for [clomiPRAMINE](#)). Efficacy was



assessed according to the Yale-Brown Obsessive Compulsive Scale and Clinical Global Impression Scale. [Fluvoxamine](#) was better tolerated, with less anticholinergic adverse effects while [clomiPRAMINE](#) had a quicker onset of action. Further studies are needed to demonstrate a time-related effect that might differentiate these drugs [616].

#### 4.6.L.5] [Panic disorder](#)

a) [ClomiPRAMINE](#) (10 milligrams (mg) for three days and 20 mg for four days) and [fluvoxamine](#) (50 mg/day for seven days) were both effective in decreasing the hypersensitivity to 35% carbon dioxide, supporting the serotonergic effect of these drugs to decrease panic attacks through modification of carbon dioxide sensitivity. Thirty-nine [panic disorder](#) patients were enrolled in a double-blind, randomized, placebo-controlled study, where each patient was given the 35% carbon dioxide challenge on days 0, 3, and 7. Patients on [clomiPRAMINE](#) and [fluvoxamine](#) showed significant reduction in sensitivity over placebo after seven days as seen by the percent change on a visual analogue for anxiety scale ( $p=0.027$ ) [617].

#### 4.6.M] [Haloperidol](#)

##### 4.6.M.1] [Autistic disorder](#)

a) Among subjects who completed full therapeutic trials of [haloperidol](#) and [clomiPRAMINE](#) for treatment of [autistic disorder](#), the two drugs were comparable; however, [haloperidol](#) was superior to [clomiPRAMINE](#) on an intent-to-treat basis, because of the large proportion of patients who were unable to complete [clomiPRAMINE](#) treatment due to side effects and behavior problems. In a double-blind, placebo-controlled crossover study, 36 subjects with a DSM-IV diagnosis of [autism](#) were given placebo, [haloperidol](#), and [clomiPRAMINE](#) for periods of 7 weeks each. [ClomiPRAMINE](#) was begun at 25 milligrams (mg) at bedtime for 2 days and increased to 25 mg twice a day for 2 days, 25 mg 3 times a day for 2 days, and finally 50 mg twice a day. [Haloperidol](#) was begun at 0.25 mg at bedtime for 2 days and increased to 0.25 mg twice a day for 2 days, 0.25 mg 3 times a day for 2 days, and finally 0.5 mg twice a day. For both drugs, adjustments of the final dose could be made as clinically indicated. During week 7 of each period, drug dosages were tapered in preparation for the next treatment. Percentages of subjects completing each trial were 70% for [haloperidol](#), 38% for [clomiPRAMINE](#), and 66% for placebo. In the [haloperidol](#) trials, 7 of 10 discontinuations were for side effects (fatigue or lethargy, [dystonia](#), depression) and the remainder for behavior problems. With [clomiPRAMINE](#), 12 of 20 discontinuations were for side effects (fatigue or lethargy, tremors, [tachycardia](#), insomnia, diaphoresis, nausea or vomiting, and decreased appetite) and the remainder for behavior problems. In the placebo trials, 10 of 11 discontinuations were for behavior problems. On an intent-to-treat basis, significant improvement in irritability ( $p$  less than 0.05) and hyperactivity ( $p$  less than 0.05) was seen with [haloperidol](#) only (versus baseline). No differences among treatments were observed for stereotypic behavior, lethargy, or inappropriate speech. When data only from patients completing full therapeutic trials were assessed, both [haloperidol](#) and [clomiPRAMINE](#) were superior to baseline with regard to irritability and stereotypy [619].

#### 4.6.N] [Imipramine](#)

##### 4.6.N.1] [Depression](#)

a) [ClomiPRAMINE](#) was as effective as [imipramine](#) in treating depression in 24 patients during a 44-day, randomized, double-blind study [651]. The patients were diagnosed with [psychotic depression](#) independently by 2 psychiatrists. Oral [imipramine](#) or oral [clomiPRAMINE](#) was administered 3 times daily in 50 milligram doses. Throughout the study periodic assessments using the Hamilton Depression Rating Scale and the [Beck Depression Inventory](#) demonstrated a significant reduction in depression from baseline for both drugs; however, a significant difference in antidepressant effects between drugs could not be seen.

Minor and transient anticholinergic adverse effects were noted in all patients and included blurred vision, dry mouth, increased sweating, hand tremor, and dizziness. Three patients dropped out of the study, but none of these was due to adverse effects.

#### 4.6.N.2] Obsessive-compulsive disorder

a) SUMMARY: ClomiPRAMINE is superior to imipramine in the treatment of obsessive-compulsive disorder.

b) Oral clomiPRAMINE was slightly superior to oral imipramine in improving symptoms of obsessive-compulsive disorder [652]. A 12-week, double-blind study of 23 patients according to DSM-III with secondary depression diagnosed was conducted to compare the 2 drugs. Both drugs were started at 50 milligrams/day; this was gradually increased to 300 mg/day as tolerated. Seven patients did not complete the study: 4 because of adverse effects (2 from each group), 2 because of unsatisfactory therapeutic response with imipramine, and 1 for no apparent reason. Both drugs produced improvement in depressive symptoms; however, only clomiPRAMINE demonstrated improvement in obsessive symptoms when compared to baseline. Typical anticholinergic adverse effects were experienced by both treatment groups with no significant differences between the two. It is difficult to accurately evaluate the clinical response in this study because of the small number of patients and the methods used for statistical analysis.

c) Both oral clomiPRAMINE and oral imipramine were effective in improving symptoms in obsessive-compulsive disorder patients who met DSM-III criteria [653]. The study was a 12-week, double-blind trial that compared the efficacy of clomiPRAMINE and imipramine in treating obsessive-compulsive disorders. Both drugs were begun at 25 to 50 milligrams/day; this was increased to 300 mg/day as tolerated. At the end of the trial, the mean daily dose of both drugs was 220 mg. Two of 3 clomiPRAMINE-treated patients and 2 of 5 imipramine-treated patients were classified as responders. For both drugs, maximal improvement in depression was evident at 4 weeks, while maximal improvement in obsessive-compulsive symptoms was not seen until 8 weeks. The responders also had higher pretreatment depression scores than did nonresponders, which corresponded with the results of another study [654]. Because of the small sample size, differences (n=8) in efficacy between clomiPRAMINE and imipramine could not be determined.

d) The relationship between the antiobsessional and antidepressant effects of tricyclic drugs was studied in primary obsessive-compulsive disorder. Study 1 consisted of a controlled 12-week trial with clomiPRAMINE (n=7) and placebo (n=5); study 2 analyzed the pooled data from 15 uniformly selected patients who were treated with either clomiPRAMINE or imipramine. Although the antiobsessional and antidepressant effects of the drugs covaried, antidepressant action was not a prerequisite for antiobsessional effects. ClomiPRAMINE, and probably imipramine, possess specific antiobsessive effects that are at least partially independent of the antidepressant effects [653].

#### 4.6.O] Lithium

##### 4.6.O.1] Depression

a) The effects of lithium and clomiPRAMINE (CMI) on signs and symptoms were compared in 22 patients with major depression [627]. They also compared effects of the two drugs on serum calcium and magnesium. Evaluation of response using the Comprehensive Psychopathological Rating Scale (CPRS) and side effects was made after a 5 to 7 day placebo period, at 2 weeks and at 4 weeks of treatment. After 2 weeks of treatment, the rated scores dropped for more than half of the CPRS items. After 4 weeks, the scores for all but one item were reduced in both groups and after 4 weeks global scores were also reduced. There was no significant difference between lithium patients and CMI patients in response at 2 and 4 weeks. Lithium treatment was associated with fluctuations in calcium and magnesium levels in plasma but there were no changes in CMI patients. Serum prolactin increased during CMI treatment but was unaffected by lithium treatment. There was no correlation between rating scores and drug blood levels, serum prolactin, calcium or magnesium.

#### 4.6.P] Lofepramine

##### 4.6.P.1] Depression

a) A meta-analysis of 4 studies comparing lofepramine (n=79) with **clomiPRAMINE** (n=79) concluded that lofepramine was superior to **clomiPRAMINE** in efficacy and tolerance [623]. Overall, there was a significant difference between the number of lofepramine-treated patients (62%) and **clomiPRAMINE**-treated patients (37%) who improved during the 6-week trials. Fewer patients reported side effects with lofepramine than **clomiPRAMINE** (54% vs 65%; p less than 0.15). Lofepramine doses ranged from 70 to 210 milligrams/d, and **clomiPRAMINE** doses ranged from 50 to 150 milligrams/d.

b) Oral lofepramine 70 milligrams twice daily was slightly superior to oral **clomiPRAMINE** 50 milligrams twice daily in a 6-week, randomized, double-blind study involving 60 depressed patients. Lofepramine-treated patients demonstrated a significantly greater improvement on the Hamilton Depression Scale than **clomiPRAMINE** by the end of the study. Statistical significance between the 2 drugs could not be determined in the Self-Rating Depression Scale. Typical mild anticholinergic effects were experienced by both groups, with no significant differences between the drugs [624].

#### 4.6.Q] Maprotiline

##### 4.6.Q.1] Depression

a) **Maprotiline** and **clomiPRAMINE** were equally effective in a 4-week, randomized, double-blind study in 12 depressed patients [605]. All patients were endogenously depressed; however, diagnosis criteria was not discussed. Both drugs were started orally at 75 milligrams/day; this was increased to 225 mg/day after 2 weeks if 150 mg/day was inadequate. The Hamilton Depression Rating Scale was used to assess therapeutic efficacy. At the end of the study, both drugs improved depression symptoms to a similar degree and no difference in efficacy could be distinguished. The **clomiPRAMINE**-treated patients appeared to improve sooner than the **maprotiline**-treated patients. Adverse effects were generally mild and similar for both drugs: dry mouth, constipation, and tremor. Because of the small number of patients and short duration of the study, further studies are required to adequately compare the 2 drugs in the treatment of depression.

##### 4.6.Q.2] Pain, Idiopathic

a) Oral **clomiPRAMINE** (mean 97 milligrams/day) was more effective in reducing the overall idiopathic pain syndrome symptoms than oral **maprotiline** (mean 100 milligrams/day) during a 6-week, randomized, double-blind study of 52 patients [606]. An overall improvement was seen in 63% of the **clomiPRAMINE**-treated patients and in only 36% of the **maprotiline**-treated patients. **ClomiPRAMINE** produced improvements in pain, **memory disturbances**, concentration difficulties, inner tension, sadness, and bodily discomfort. The most common adverse effect for both drugs was dry mouth, while sweating was more prevalent with **clomiPRAMINE**. Eight **clomiPRAMINE** patients withdrew from the study because of adverse effects compared to only 1 **maprotiline**-treated patient.

#### 4.6.R] Metoprolol

##### 4.6.R.1] Migraine

a) **Metoprolol**, in oral doses up to 100 milligrams/day, was superior to oral **clomiPRAMINE** (up to 100 milligrams/day) and placebo in 63 migraine headache sufferers during a 16-week, randomized, double-blind, crossover study [620]. All patients were diagnosed with common or **classic migraines** according to the Ad Hoc Committee on Classification of Headache. The drugs were administered at 4-week intervals, with 4-week washout periods before crossover. **Metoprolol** was the only agent that significantly reduced

both the frequency and duration of migraine attacks. When compared to placebo, [clomiPRAMINE](#) had no influence on migraine attacks. Adverse effects from [clomiPRAMINE](#) caused 18 patients to discontinue treatment. The most commonly reported adverse effects with [clomiPRAMINE](#) included insomnia, sweating, tiredness, and constipation.

#### 4.6.S] Mianserin

##### 4.6.S.1] Depression

a) SUMMARY: Comparative clinical trials with mianserin and fail to demonstrate any significant differences in antidepressant activity. [ClomiPRAMINE](#) may produce more adverse effects than mianserin.

b) Oral mianserin 60 mg daily and oral [clomiPRAMINE](#) 150 mg daily were compared for antidepressant activity during a 4-week, multicenter, randomized, double-blind study of 145 depressed patients [639]. At the end of the trial, both drugs produced significant but indistinguishable improvement in depression. The [clomiPRAMINE](#) patients demonstrated a slightly significant increase in adverse effects that were mild and included dry mouth, hypotension, and tremor. Ten patients, 4 on mianserin and 6 on [clomiPRAMINE](#), did not complete the study because of drug-related problems; these included adverse effects, clinical deterioration, and increased suicidal risk.

c) A 5-week, randomized, double-blind study compared the safety and efficacy of mianserin and [clomiPRAMINE](#) in 42 patients with primary [unipolar depression](#) according to the International Classification of Diseases [640] [641]. Patients were started on either oral mianserin 30 milligrams or oral [clomiPRAMINE](#) 75 milligrams once daily; both doses were doubled beginning in the second week. Both groups demonstrated significant improvement in depression symptoms; however, the mianserin group demonstrated slightly more improvement after 5 weeks of therapy. Adverse effects were similar in both groups, but more prevalent in the [clomiPRAMINE](#) group, and included dry mouth, tremor, [tachycardia](#), dizziness, excitement, and nasal congestion. [Tachycardia](#) and excitement were only present in the [clomiPRAMINE](#) group. One mianserin patient and 5 [clomiPRAMINE](#) patients withdrew from the study because of adverse effects.

d) The antidepressant activity of oral mianserin 30 to 60 milligrams daily and oral [clomiPRAMINE](#) 75 to 150 milligrams daily was compared in 62 mildly depressed patients during a 4-week, randomized, double-blind study [642]. No significant difference in antidepressant activity could be demonstrated between the 2 drugs. Similar anticholinergic adverse effects were experienced by both groups; however, [clomiPRAMINE](#) patients reported more tremor, dry mouth, [tachycardia](#), and dizziness and 2 withdrew from the study because of adverse effects.

##### 4.6.S.2] Headache

a) Mianserin, [clomiPRAMINE](#), and placebo were studied in a double-blind, parallel group comparison involving 82 patients with chronic tension headaches. Both mianserin and [clomiPRAMINE](#) produced improvements in pain scores in light of a significant placebo response after 6 weeks of therapy with either oral [clomiPRAMINE](#) 75 to 150 milligrams/day or mianserin 30 to 60 milligrams/day [643].

##### 4.6.S.3] Pain

a) No significant difference was found among oral [clomiPRAMINE](#) (75 to 150 milligrams/day), mianserin (30 to 60 milligrams/day), and placebo in a study of 253 patients with chronic idiopathic pain syndrome. Improvement rate was about 40% after 6 weeks when using a 50% or better reduction in pain level. In patients who fulfilled checklist criteria for minor-to-major depression (30% of patients), [clomiPRAMINE](#) was superior to mianserin and placebo, with an improvement rate of 75% after 7 weeks. Both mianserin and [clomipramine](#) were superior to placebo in patients with low back pain. No difference among the 3 treatments was found in patients with burning mouth syndrome or abdominal pain [644].

#### 4.6.T] Milnacipran

##### 4.6.T.1] Depression

- a) Milnacipran offers no efficacy advantage over tricyclic antidepressants. Milnacipran 50 to 100 mg twice daily has been comparable to or less effective than [imipramine](#) 100 to 150 mg daily, [amitriptyline](#) 150 mg daily, and [clomiPRAMINE](#) 75 to 150 mg daily in the treatment of [major depressive disorders](#); primary endpoints were improvements on the Hamilton and Montgomery-Asberg scales [632] [633] [634] [635] [636] [637]. A more rapid onset of action has been observed with [clomiPRAMINE](#) and [amitriptyline](#) [633] [637].
- b) Greater improvement of CGI-3 scores (therapeutic index, incorporating efficacy and tolerance) was reported with milnacipran in a manufacturer-prepared meta analysis of tricyclic antidepressant comparative trials [635] [634], and this appears in manufacturer product information. However, statistical significance between treatments was not demonstrated [635].

#### 4.6.U] Moclobemide

##### 4.6.U.1] Depression

- a) SUMMARY: [ClomiPRAMINE](#) and moclobemide have been similarly effective in the treatment of depression; a faster onset of action and lower incidence of adverse effects have been reported with moclobemide in some studies. Drop-out rates due to clinical worsening and suicidality were more likely with moclobemide than [clomiPRAMINE](#) in one study.
- b) [ClomiPRAMINE](#) in doses of 75 to 200 milligrams daily has been as effective as moclobemide 300 to 600 milligrams daily in treating endogenous and non-endogenous depression in most controlled studies [645] [646] [647]. One study [648] reported that moclobemide, [imipramine](#), and placebo were all associated with similar clinical improvement in patients with non-endogenous depression. Lack of statistical superiority of these agents over placebo in this report may have been a reflection of the small number of patients treated (20 in each group). In a larger controlled trial (n=191), moclobemide and [clomiPRAMINE](#) produced similar and significant improvement in non-endogenously depressed patients; however, placebo was not incorporated into this study [649].
- c) An advantage for moclobemide with regard to tolerability (particularly its lesser anticholinergic effects) was reported in some of these studies. However, a similar adverse effect profile for moclobemide and [clomiPRAMINE](#) emerged in others [646].
- d) The onset of antidepressant effect was quicker with moclobemide (10 days) as compared to [clomiPRAMINE](#) (13 days) in some studies [647].
- e) Antidepressant and adverse effects of moclobemide (MCB) (400 milligrams/day) and [clomiPRAMINE](#) (CMI) (150 milligrams/day) were compared in a double-blind, randomized, inpatient, fixed-dose study with weekly ratings and drug level measurements. After 1 week on single-blind treatment, 115 patients with [major depression](#) who met inclusion criteria were begun on active treatment for 6 weeks. MCB drop-outs (N=20) were primarily due to clinical worsening and suicidality (N=9) whereas CMI drop-outs were related primarily to adverse effects (N=6) with none due to clinical worsening. End-point analysis using the Hamilton Depression Scale showed a significant difference favoring CMI over MCB [650].

#### 4.6.V] Nortriptyline

##### 4.6.V.1] Pain

- a) Twenty-four patients with central pain completed a randomized, crossover, placebo-controlled study of the efficacy and tolerability of [clomiPRAMINE](#) and [nortriptyline](#). Results showed strong predominance of active drugs over placebo and a significantly more effective analgesic effect of [clomiPRAMINE](#) over



[nortriptyline](#). The analgesic effect of both tricyclic compounds is independent of any antidepressant effect [592].

#### 4.6.W| Oxaprotiline

##### 4.6.W.1| Depression

a) Oral oxaprotiline 150 milligrams/day and oral [clomiPRAMINE](#) 150 milligrams/day were compared for efficacy in the treatment of 38 depressed patients during a 4-week, randomized, double-blind study [626]. All patients were diagnosed as having either endogenous or psychogenous (psychotic) depression according to ICD (International Classification of Diseases) criteria and were divided equally between the 2 drug therapy groups. After 2 weeks of therapy, both drugs demonstrated equal improvement in depression as assessed by a trained therapist; however, after 4 weeks, the [clomiPRAMINE](#) group was slightly more improved as determined by the Hamilton Depression Rating Scale and the Self-Rating Scale of Depression. Adverse effects were generally mild and similar for both drugs; they included tremor, sweating, agitation, headaches, and dizziness. Three patients withdrew from the study: 1 from each group due to perceived lack of efficacy and the third due to a venous [thrombosis](#) that was not felt to be drug-related.

#### 4.6.X| [Paroxetine](#)

##### 4.6.X.1| Depression

a) In a large (n=1002) clinical trial, treatment with [paroxetine](#) or [clomiPRAMINE](#) produced similar decreases in anxiety and depression scores; however, adverse effects occurred in significantly (p=0.025) more patients treated with [clomiPRAMINE](#) than [paroxetine](#) [628]. Statistically significant differences between treatments were NOT found on the Montgomery-Asberg Depression Rating Scale (MADRS) or Clinical Anxiety Scale (CAS), but a trend in favor of [paroxetine](#) was observed for the Clinical Global Impressions (CGI) score at 6 and 12 weeks (p=0.015). Patients entered into this trial had depression with anxiety which was treated in a primary care setting. [Paroxetine](#) 20 milligrams (mg) daily was used initially but the protocol permitted an increase to 40 mg daily, if needed, after 4 weeks. [ClomiPRAMINE](#) titration proceeded as follows: (1) 25 mg in the evening for 3 days; (2) 50 mg in the evening for 4 days; (3) 75 mg daily (25 mg in the morning and 50 mg in the evening); and (4) after 4 weeks, the dose could be increased to 150 mg/day. Based on this study, [paroxetine](#) and [clomiPRAMINE](#) have comparable efficacy but the incidence of adverse effects (AE) including serious AE is lower in patients treated with [paroxetine](#).

b) [Paroxetine](#) 30 milligrams once daily was as effective as [clomiPRAMINE](#) 25 milligrams three times daily in the treatment of [major depressive disorder](#) in a 6-week, double-blind study involving 79 elderly patients (60 years of age or older) [629]. Anticholinergic effects and somnolence occurred to a greater degree with [clomiPRAMINE](#), whereas nausea and vomiting were observed more frequently with [paroxetine](#).

c) [ClomiPRAMINE](#) demonstrated a significantly better therapeutic effect than [paroxetine](#) using categorical response measures and group averages of rating scores during a double-blind, randomized, inpatient study of 120 depressed patients [630]. Patients were randomized to receive either [paroxetine](#) 30 milligrams/day or [clomiPRAMINE](#) 150 milligrams/day for this 6-week study. At the end of week 4, 27 patients were rated as nonresponders and were terminated from the study. Of these 27 patients, 23 were in the [paroxetine](#) group.

##### 4.6.X.2| [Obsessive-compulsive disorder](#)

a) In a 12-week, comparative study, [paroxetine](#) was as effective as [clomiPRAMINE](#) for treating [obsessive compulsive disorder](#). Patients were randomly assigned to receive placebo (n=99), [paroxetine](#) 10 milligrams (mg) (n=201), or [clomiPRAMINE](#) 25 mg daily (n=99); the dose of active treatments was titrated to a maximum of 60 mg and 250 mg for [paroxetine](#) and [clomiPRAMINE](#), respectively. No



statistically significant differences were found in the primary efficacy measures, the Yale-Brown Obsessive-Compulsive Scale or the National Institute of Mental Health Obsessive-Compulsive Scale, between [paroxetine](#) or [clomiPRAMINE](#); however, both drugs were significantly better than placebo. Adverse effects requiring treatment withdrawal occurred in fewer patients treated with [paroxetine](#) (9%;  $p=0.033$ ) than [clomiPRAMINE](#) (17%). Limitations of the study are the relatively short duration, and the potential loss of blinding due to differences in adverse effects [631].

#### 4.6.Y] [Pentazocine](#)

##### 4.6.Y.1] Postoperative pain

a) [ClomiPRAMINE](#) was as effective as [pentazocine](#) for relieving postoperative pain. Forty patients (30 to 50 years old) received either intramuscular [clomiPRAMINE](#) 50 mg or [pentazocine](#) 30 mg a half an hour after the end of [anesthesia](#) for [hysterectomies](#) or [laparotomies](#). No significant difference was observed between either agent for analgesia [607].

#### 4.6.Z] [Phenelzine](#)

##### 4.6.Z.1] [Obsessive-compulsive disorder](#)

a) [ClomiPRAMINE](#) and [phenelzine](#) had similar efficacy in a double-blind clinical trial conducted in 30 patients suffering from DSM-III [obsessive-compulsive disorder](#). The study period was 12 weeks and the maximum doses used (from the fifth week on) were 225 milligrams/d for [clomiPRAMINE](#) (14 patients) and 75 milligrams/d for [phenelzine](#) (12 patients); four patients dropped out. Obsessive symptoms improved significantly in both drug groups, but there was no significant difference between groups. Depressive symptoms responded faster than obsessive symptoms [601].

#### 4.6.AA] [Quetiapine Fumarate](#)

##### 4.6.AA.1] [Obsessive-compulsive disorder](#)

a) In a 12-week, randomized, placebo-controlled trial, the addition of [clomiPRAMINE](#) or placebo to [fluoxetine](#) was more effective than the addition of [quetiapine](#) to [fluoxetine](#) in reducing symptoms of [obsessive-compulsive disorder](#) (OCD; DSM-IV TR criteria) in adult patients refractory to [fluoxetine](#) monotherapy ( $n=54$ ). For study inclusion, all patients had a Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores of at least 16, which was also a decrease of less than 35% from baseline, despite at least 8 weeks of [fluoxetine](#) (maximum dose, 80 mg/day). Enrolled patients were randomized to receive [clomiPRAMINE](#) ( $n=18$ ; initial dose, 25 mg/day; weekly titration up to 75 mg/day; mean dose, 55 mg/day) plus [fluoxetine](#) (maximum dose, 40 mg/day), [quetiapine](#) ( $n=18$ , initial dose, 50 mg/day; weekly titration up to 200 mg/day; mean dose, 142 mg/day) plus [fluoxetine](#) (maximum dose, 40 mg/day), or placebo ( $n=18$ ) plus [fluoxetine](#) (maximum dose, 80 mg/day). Mean final YBOCS scores and the mean change from baseline at week 12 (primary endpoint; intent-to-treat), were significantly improved for both [clomiPRAMINE](#) (final score, 18; change from baseline, -6.5; 95% CI, -9 to -3.9) and placebo (final score 18; change from baseline, -6.7; 95% CI, -9.6 to -3.8) compared with [quetiapine](#) (final score, 25; change from baseline, -0.1; 95% CI, -2.9 to +2.7) ( $p$  less than 0.001 for both). Withdrawal due to adverse effects occurred in 3 patients treated with [clomiPRAMINE](#) (QT prolongation from patient-specific baseline on ECG) and in 1 patient treated with [quetiapine](#) (syncope associated with orthostatic hypotension) [15].

#### 4.6.AB] [Sildenafil](#)

##### 4.6.AB.1] [Premature ejaculation](#)

a) According to a double-blind, randomized, cross-over study (n=31), as-needed **SILDENAFIL** was superior in the treatment of **premature ejaculation** compared with **clomiPRAMINE**, **PAROXETINE**, **SERTRALINE**, and PAUSE-SQUEEZE technique. **ClomiPRAMINE**, **paroxetine**, and **sertraline** had generally similar efficacy and safety. **Paroxetine** exhibited improved efficacy and satisfaction over pause-squeeze, while efficacy and satisfaction were similar to pause-squeeze for **clomiPRAMINE** and **sertraline**. Median intravaginal ejaculation latency time (IVELT) increased significantly to 4 minutes (min), 4 min, 3 min, 15 min, and 3 min from baseline 1 min for **clomiPRAMINE**, **paroxetine**, **sertraline**, **sildenafil**, and pause-squeeze, respectively (all p less than 0.0001). **Paroxetine** was superior to pause-squeeze with respect to IVELT (p=0.04) and sexual satisfaction (p=0.025). A significant positive correlation occurred between ejaculation latency and sexual satisfaction. No significant differences in adverse effects were found among the 4 drugs. Three patients dropped out due to side effects, including **sildenafil** (2) and **clomiPRAMINE** (1; also lack of efficacy in this patient). Three additional patients dropped out due to lack of efficacy related to **clomiPRAMINE**, **paroxetine**, **sertraline**, and/or pause-squeeze. Medications were administered as needed 3 to 5 hours before planned intercourse and not more than twice a week. Doses were **clomiPRAMINE** 25 milligrams (mg), **paroxetine** 20 mg, **sertraline** 50 mg, and **sildenafil** 50 mg [618].

#### 4.6.AC] **Venlafaxine**

##### 4.6.AC.1] **Depression**

a) **Venlafaxine** 105 milligrams/day (average dose) tended to be more effective than **clomiPRAMINE** 105 milligrams/day (average dose) for the treatment of depression in a 6-week study with 102 patients; however, the difference was not statistically significant [608]. Patients were assessed using the Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impressions scale. **Venlafaxine** was associated with fewer anticholinergic side effects and a greater incidence of headache/nausea than **clomiPRAMINE**.

## 6.0] **References**

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- 287 Product Information: KADIAN(R) oral extended-release capsules, morphine sulfate oral extended-release capsules. Actavis Pharma, Inc. (per FDA), Parsippany, NJ, 2014.
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