

DRUGDEX-EV 0204

MICROMEDEX

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## IMIPRAMINE

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

### 0.0] Overview

#### 1) Class

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

Antidepressant  
Antidepressant, Tricyclic  
Urinary [Enuresis](#) Agent

#### 2) Dosing Information

a) [Imipramine](#) Hydrochloride

##### 1) Adult

a) Depression

1) (hospitalized patients) 100 mg ORALLY per day in divided doses; may increase up to a MAX of 300 mg/day [1]

2) (outpatients) 75 mg ORALLY per day; may increase up to a MAX of 200 mg/day; usual maintenance dose, 50 to 150 mg/day [1].

b) [Panic disorder](#)

1) 100-200 mg ORALLY in divided doses (1-3 doses per day), higher doses may be required if agoraphobia is present

c) [Urinary incontinence](#)

1) 25 mg ORALLY at bedtime, may increase in 25 mg increments to max dose of 150mg at bedtime

## 2)) Pediatric

a)) safety and effectiveness in children with nocturnal [enuresis](#) below the age of 6 years have not been established; effectiveness in pediatric patients for any other condition has not been established [1]

### 1)) Nocturnal enuresis

a)) (children 6 to 12 y) initial, 25 mg ORALLY 1 h before bedtime, may increase in 25 mg increments to MAX dose of 50 mg/d or 2.5 mg/kg/d [1]

b)) (children over 12 y) initial, 25 mg ORALLY 1 h before bedtime, may increase in 25 mg increments to MAX dose of 75 mg/d or 2.5 mg/kg/d [1]

## b)) [Imipramine](#) Pamoate

### 1)) Adult

#### a)) Depression

1)) (hospitalized patients) initial, 100 to 150 mg ORALLY once daily at bedtime; may increase up to MAX of 300 mg/day; usual maintenance dose, 75 to 150 mg ORALLY once daily at bedtime [117]

2)) (outpatients) 75 mg ORALLY once daily at bedtime; may increase up to a max of 200 mg/day; usual maintenance dose, 75 to 150 mg ORALLY once daily at bedtime [117]

#### b)) [Panic disorder](#)

1)) 100-200 mg/day ORALLY in divided doses (1-3 doses per day), higher doses may be required if agoraphobia is present

## 2)) Pediatric

a)) safety and effectiveness have not been established in children [117]

## 3)) Contraindications

### a)) [Imipramine](#) Hydrochloride

1)) coadministration with a MAOI or use within 14 days of discontinuing a MAOI; may cause serious reactions (eg, hyperpyretic crisis, convulsive seizures, death) [119]

2)) hypersensitivity to dibenzazepines; risk of [cross-sensitivity reactions](#) [119]

3)) hypersensitivity to [imipramine](#) hydrochloride [119]

4)) [myocardial infarction](#), during the acute recovery period [119]

**b) Imipramine Pamoate**

- 1) coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (eg, hyperpyretic crisis, severe convulsive seizures, death) [120]
- 2) hypersensitivity to dibenzazepines; risk of [cross-sensitivity reactions](#) [120]
- 3) hypersensitivity to [imipramine](#) pamoate [120]
- 4) [myocardial infarction](#), during the acute recovery period [120]

**4) Serious Adverse Effects**

**a) Imipramine**

- 1) [Agranulocytosis](#)
- 2) [Bone marrow depression](#)
- 3) [Cardiac dysrhythmia](#)
- 4) Dead - sudden death
- 5) Depression, worsening
- 6) [Fulminant hepatic failure](#)
- 7) [Heart failure](#)
- 8) [Hepatitis](#)
- 9) [Immune hypersensitivity reaction](#)
- 10) [Jaundice](#)
- 11) Mania
- 12) Nephrotoxicity
- 13) Prolonged QT interval
- 14) Seizure
- 15) Suicidal thoughts
- 16) Suicide

**b) Imipramine Hydrochloride**

- 1) [Agranulocytosis](#)
- 2) Atrioventricular conduction pattern - finding
- 3) [Cardiac dysrhythmia](#)

- 4)) Cerebrovascular accident
- 5)) Decreased liver function
- 6)) Depression, worsening
- 7)) [Heart block](#)
- 8)) [Hypertension](#)
- 9)) [Jaundice](#)
- 10)) [Myocardial infarction](#)
- 11)) Orthostatic hypotension
- 12)) Palpitations
- 13)) Prolonged QT interval
- 14)) [Psychotic disorder](#)
- 15)) Seizure
- 16)) Suicidal thoughts
- 17)) Suicide
- 18)) Syncope

c) [Imipramine](#) Pamoate

- 1)) [Agranulocytosis](#)
- 2)) Atrioventricular conduction pattern - finding
- 3)) [Cardiac dysrhythmia](#)
- 4)) [Cardiac dysrhythmia](#)
- 5)) Cerebrovascular accident
- 6)) Decreased liver function
- 7)) Depression, worsening
- 8)) [Hypertension](#)
- 9)) [Jaundice](#)
- 10)) [Myocardial infarction](#)
- 11)) Orthostatic hypotension
- 12)) Prolonged QT interval

13) Seizure

14) Suicidal thoughts

15) Suicide

16) Syncope

## 5) Clinical Applications

### a) [Imipramine](#) Hydrochloride

#### 1) FDA Approved Indications

a) Depression

b) Nocturnal [enuresis](#)

#### 2) Non-FDA Approved Indications

a) [Panic disorder](#)

b) [Urinary incontinence](#)

### b) [Imipramine](#) Pamoate

#### 1) FDA Approved Indications

a) Depression

#### 2) Non-FDA Approved Indications

a) [Panic disorder](#)

## 1.0] Dosing Information

[Drug Properties](#)

[Storage and Stability](#)

[Adult Dosage](#)

[Pediatric Dosage](#)

### 1.1] Drug Properties

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

B) Synonyms

[Imipramine](#)

[Imipramine](#) HCl

[Imipramine](#) Hydrochloride

[Imipramine](#) Pamoate

## 1.2] Storage and Stability

### A) Oral route

1) Store between 59 and 86 degrees F (15 to 30 degrees C) [226].

### B) Parenteral route

1) Store between 59 to 86 degrees F (15 to 30 degrees C). Upon storing, minute crystals may form; this has no influence on the drug's therapeutic efficacy. Crystals will dissolve when the ampul is immersed in hot water [226][39][24].

## 1.3] Adult Dosage

### 1.3.1] Normal Dosage

#### 1.3.1.A] Imipramine

##### 1.3.1.A.1] Cataplexy - Narcolepsy

See Drug Consult reference: [NARCOLEPSY AND CATAPLEXY - DRUG THERAPY](#)

#### 1.3.1.B] Imipramine Hydrochloride

##### 1.3.1.B.1] Intramuscular route

###### 1.3.1.B.1.a] Depression

1) Initial intramuscular dose of up to 100 milligrams/day in divided doses. Lower dosages are recommended in adolescents and for outpatients [2][23][24].

##### 1.3.1.B.2] Oral route

###### 1.3.1.B.2.a] Agoraphobia

1) Efficacy is dose related and may require doses of 150 milligrams/day or greater [59]; (Mavissaakalian & Perel, 1985a)[63][61].

###### 1.3.1.B.2.b] Bulimia nervosa

1) The doses used in the treatment of [bulimia](#) have ranged from the doses commonly used in the treatment of depression (75 to 275 milligrams/day) [66][67][68].

###### 1.3.1.B.2.c] Depression

###### 1) HOSPITALIZED PATIENTS

a) The recommended initial dose for hospitalized patients is 100 milligrams (mg) orally per day in divided doses and gradually increased to 200 mg/day as required. If no response is seen after 2 weeks, then the dose may be increased up to 250 to 300 mg ORALLY per day in divided doses [1]. Doses as high as 750 milligrams/day maintenance in divided doses have been reported [20] but are not recommended.

###### 2) OUTPATIENTS

a) The recommended initial dose for outpatients is 75 milligrams (mg) orally per day, increased to 150 mg per day. Usual maintenance dose ranges from 50 to 150 mg daily. The recommended maximum dose is 200 mg/day [1].

b) Maintenance doses greater than 150 milligrams/day have been well tolerated and may be required in some patients to prevent relapses, but are associated with a higher incidence of persistent side effects (ie, dizziness, headache, nausea, and vomiting) [21]. The best method, other than experience, for determining the optimal maintenance dose for a particular individual has not been established.

c) Patients with chronic depression that respond to imipramine may benefit from long-term maintenance therapy [22].

#### 1.3.1.B.2.d] Diabetic neuropathy

1) Standard doses of 100 milligrams/day of imipramine may not be high enough to produce therapeutic benefit in some patients with diabetic neuropathy. In one study, the therapeutic dose range was 125 milligrams/day to 350 milligrams/day. The maximum therapeutic effect in neuropathy is reached within a week. Dosage titration should be started with a dose corresponding to a plasma level of 100 to 200 nmol/L for imipramine plus desipramine. The dose should then be increased in a stepwise fashion [69].

#### 1.3.1.B.2.e] Panic disorder

1) Based upon a dose-response study in patients with panic disorder with agoraphobia, IMIPRAMINE in moderate doses of 1.5 milligrams/kilogram/day (approximately 100 milligrams daily) may be effective in the treatment of panic in some patients, whereas higher doses (3 milligrams/kilogram/day, approximately 200 milligrams daily) may be optimal for the agoraphobic dimension of this disorder [52]; (Mavissakalian & Peral, 1994)[53].

2) The suggested target dose is 2.25 milligrams/kilogram/day or a total (imipramine and N-desmethylimipramine) plasma concentration of 110 to 140 nanograms/milliliter in the acute treatment of patients with panic disorder with agoraphobia. Higher doses were associated with good clinical response but a greater dropout rate secondary to side effects (Mavissakalian & Peral, 1995).

#### 1.3.1.B.2.f] Urinary incontinence

1) The dose used in the treatment of urinary incontinence is 75 to 150 milligrams/day. The dose can be started at 25 milligrams per day and titrated to clinical effect. Some patients may require the dose to be administered in divided doses throughout the day instead of single dose administration [58][55]; (Castleden et al, 1981)[56].

2) Imipramine 25 milligrams three times daily has been used in the treatment of females with urinary incontinence due to detrusor instability [56].

### 1.3.1.C] Imipramine Pamoate

#### 1.3.1.C.1] Oral route

##### 1.3.1.C.1.a] Agoraphobia

1) Efficacy is dose related and may require doses of 150 milligrams/day or greater [59]; (Mavissakalian & Peral, 1985a)[63][61].

**1.3.1.C.1.b) Bulimia nervosa**

1)) The doses used in the treatment of bulimia have ranged from the doses commonly used in the treatment of depression (75 to 275 milligrams/day) [66][67][68].

**1.3.1.C.1.c) Depression****1)) HOSPITALIZED PATIENTS**

a)) The initial oral dose for hospitalized patients is usually 100 to 150 milligrams (mg) once daily at bedtime and may be increased to 200 mg/day as required. If no response is seen after 2 weeks, then the dose may be increased up to 250 to 300 mg/day. Doses greater than 150 mg daily may be administered once a day after the optimum dosage and tolerance have been determined. The usual maintenance dose ranges from 75 to 150 mg once daily at bedtime [117]. Doses as high as 750 milligrams/day maintenance in divided doses have been reported [20] but are not recommended.

**2)) OUTPATIENTS**

a)) The usual initial oral dose for outpatients is 75 milligrams (mg) once daily at bedtime and may be increased up to 200 mg/day. Doses greater than 75 mg daily may be administered once a day after the optimum dosage and tolerance have been determined. The usual maintenance dose ranges from 75 to 150 mg once daily at bedtime [117].

b)) Maintenance doses greater than 150 milligrams/day have been well tolerated and may be required in some patients to prevent relapses, but are associated with a higher incidence of persistent side effects (ie, dizziness, headache, nausea, and vomiting) [21]. The best method, other than experience, for determining the optimal maintenance dose for a particular individual has not been established.

c)) Patients with chronic depression that respond to imipramine may benefit from long-term maintenance therapy [22].

**1.3.1.C.1.d) Diabetic neuropathy**

1)) Standard doses of 100 milligrams/day of imipramine may not be high enough to produce therapeutic benefit in some patients with diabetic neuropathy. In one study, the therapeutic dose range was 125 milligrams/day to 350 milligrams/day. The maximum therapeutic effect in neuropathy is reached within a week. Dosage titration should be started with a dose corresponding to a plasma level of 100 to 200 nmol/L for imipramine plus desipramine. The dose should then be increased in a stepwise fashion [69].

**1.3.1.C.1.e) Panic disorder**

1)) Based upon a dose-response study in patients with panic disorder with agoraphobia, IMIPRAMINE in moderate doses of 1.5 milligrams/kilogram/day (approximately 100 milligrams daily) may be effective in the treatment of panic in some patients, whereas higher doses (3 milligrams/kilogram/day, approximately 200 milligrams daily) may be optimal for the agoraphobic dimension of this disorder [52]; (Mavissakalian & Peral, 1994)[53].

2)) The suggested target dose is 2.25 milligrams/kilogram/day or a total (imipramine and N-desmethylimipramine) plasma concentration of 110 to 140 nanograms/milliliter in the acute treatment of patients with panic disorder with agoraphobia. Higher doses were associated with



good clinical response but a greater dropout rate secondary to side effects (Mavissakalian & Peral, 1995).

### 1.3.2] Dosage in Renal Failure

#### A) Imipramine Hydrochloride

1) No specific dosage adjustment is necessary [111].

#### B) Imipramine Pamoate

1) No specific dosage adjustment is necessary [111].

### 1.3.4] Dosage in Geriatric Patients

#### A) Imipramine Hydrochloride

##### 1) GENERAL INFORMATION

a) Dosage reduction is recommended in elderly patients since this patient population is reported to have an increased incidence of confusional-type reactions and other central nervous system symptoms while on tricyclic antidepressant therapy [112]. A one-third to one-half reduction in tricyclic antidepressant dosage is suggested in the elderly. An increase in age is correlated with elevated steady-state serum levels of imipramine, desipramine and amitriptyline [113][114].

##### 2) DEPRESSION

a) The initial recommended dose for depression in geriatric patients is 30 to 40 milligrams orally daily; it is generally not necessary to exceed 100 milligrams/day [1].

##### 3) URINARY INCONTINENCE

a) In elderly patients with urinary incontinence associated with spontaneous unstable detrusor contraction the dose of imipramine is started at 25 milligrams at bedtime and increased by 25 milligrams, until the patient is continent, experiences side effects, or reaches 150 milligrams/day (Castleden et al, 1981).

b) A review for utilizing antidepressants in the treatment of depression in geriatric patients has been published [115].

#### B) Imipramine Pamoate

##### 1) GENERAL INFORMATION

a) Dosage reduction is recommended in elderly patients since this patient population is reported to have an increased incidence of confusional-type reactions and other central nervous system symptoms while on tricyclic antidepressant therapy [112]. A one-third to one-half reduction in tricyclic antidepressant dosage is suggested in the elderly. An increase in age is correlated with elevated steady-state serum levels of imipramine, desipramine and amitriptyline [113][114].

b)) It is recommended that therapy in geriatric patients is initiated with [imipramine](#) hydrochloride tablets (30 to 40 milligrams orally per day [1]) since lower dosages should be used. [Imipramine](#) pamoate capsules may be used once a total daily dosage of 75 mg or higher is established [117].

### 1.3.5] Dosage Adjustment During Dialysis

#### A)) [Imipramine](#) Hydrochloride

##### 1)) [HEMODIALYSIS](#)

a)) No dosage supplementation is required following [hemodialysis](#) or [peritoneal dialysis](#) [111].

##### 2)) [PERITONEAL DIALYSIS](#)

a)) No dosage supplementation is required following [hemodialysis](#) or [peritoneal dialysis](#) [111].

#### B)) [Imipramine](#) Pamoate

##### 1)) [HEMODIALYSIS](#)

a)) No dosage supplementation is required following [hemodialysis](#) or [peritoneal dialysis](#) [111].

##### 2)) [PERITONEAL DIALYSIS](#)

a)) No dosage supplementation is required following [hemodialysis](#) or [peritoneal dialysis](#) [111].

### 1.3.6] Dosage in Other Disease States

#### A)) [Imipramine](#) Hydrochloride

##### 1)) [DIABETES](#)

a)) Studies in mice have shown that [imipramine](#) stimulates [insulin](#) secretion in the presence of low glucose concentrations, whereas it inhibits [insulin](#) secretion in the presence of high glucose levels. [Imipramine](#) should be administered with caution to type II diabetic patients [116].

#### B)) [Imipramine](#) Pamoate

##### 1)) [DIABETES](#)

a)) Studies in mice have shown that [imipramine](#) stimulates [insulin](#) secretion in the presence of low glucose concentrations, whereas it inhibits [insulin](#) secretion in the presence of high glucose levels. [Imipramine](#) should be administered with caution to type II diabetic patients [116].

## 1.4] Pediatric Dosage

### 1.4.1] Normal Dosage

#### 1.4.1.A] [Imipramine](#)

**1.4.1.A.1] Anorexia nervosa**

See Drug Consult reference: [ANOREXIA NERVOSA - DRUG THERAPY](#)

**1.4.1.B] Imipramine Hydrochloride****1.4.1.B.1] Oral route****1.4.1.B.1.a] Attention deficit hyperactivity disorder, predominantly inattentive type**

1) The dose used ranges from 25 to 100 milligrams/day and tends to be lower than those needed to treat depression. Children tend to respond within 24 hours after initiating therapy. The monitoring of serum [imipramine](#) and [desipramine](#) levels may be useful. The serum levels associated with reported responses have been 10 to 54 nanograms/milliliter of [imipramine](#) and 10 to 65 nanograms/milliliter of [desipramine](#) (Hussey & Wright, 1970)[73][74][75].

**1.4.1.B.1.b] Depression**

1) For the treatment of depression in children the initial starting dose of [imipramine](#) is 1.5 milligrams/kilogram/day given in 1 to 4 divided doses with dosage increased 1 milligram/kilogram every 3 to 4 days. The daily dose of [imipramine](#) should not exceed 5 milligrams/kilogram/day, and children receiving doses of 3.5 milligrams/kilogram/day or more should be closely monitored [25].

2) Adolescents should initially receive 30 to 40 milligrams/day. Dosages exceeding 100 mg/day are generally not necessary [1].

**1.4.1.B.1.c] Nocturnal enuresis**

1) Children, aged 6 and over, should initially receive 25 milligrams orally, 1 hour before bedtime. If satisfactory response does not occur within 1 week, the dose may be increased by 25 milligrams/day: children under 12 may receive a maximum daily dose of 50 milligrams and children over 12 may receive 75 milligrams [2][25].

2) In early-night bedwetters, it is more effective to give the drug earlier and in divided doses, ie, 25 milligrams in afternoon and then at bedtime [2].

3) The daily dose of [imipramine](#) should not exceed 2.5 milligrams/kilogram, or 50 milligrams at bedtime if 6 to 12 years of age, or 75 milligrams at bedtime if 12 years of age or older [2][25][39].

4) The optimization of [imipramine](#) dose in the treatment of [enuresis](#) should be guided by clinical response and serum [imipramine/desipramine](#) levels. The use of serum [imipramine/desipramine](#) levels may help determine non-compliance with the drug regimen and outliers. The use of a Bayesian dosing method offers no major advantages over any other method used in combination using serum level data. However, the Bayesian method may be useful to identify outliers, possible analytical errors, noncompliance, and non-steady state serum concentrations [27].

**1.4.1.C] Imipramine Pamoate****1.4.1.C.1] Oral route****1.4.1.C.1.a] Depression**

1) [Tofranil-PM\(R\)](#) should not be used in children because of the increased potential for overdose due to the high capsule potency (75 mg, 100 mg, 125 mg and 150 mg capsule) [117].

**1.4.2] Dosage in Renal Failure****A) Imipramine Hydrochloride**

1) No specific dosage adjustment is necessary [111].

**B) Imipramine Pamoate**

1) No specific dosage adjustment is necessary [111].

**1.4.4] Dosage Adjustment During Dialysis****A) Imipramine Hydrochloride****1) HEMODIALYSIS**

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis [111].

**2) PERITONEAL DIALYSIS**

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis [111].

**B) Imipramine Pamoate****1) HEMODIALYSIS**

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis [111].

**2) PERITONEAL DIALYSIS**

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis [111].

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

a) Depression, oral: 7 to 21 days [996]; (Greenblatt & Shader, 1975).

**2) Peak Response**

a) Depression, oral: 4 to 6 weeks [997].

**2.2] Drug Concentration Levels**

**A) Therapeutic Drug Concentration**

- 1) **Endogenous depression**, greater than 200 ng/mL (**IMIPRAMINE** plus **DESIPRAMINE**) [999][1000].
- 2) Prepubertal depressive symptoms, 200 to 225 ng/mL (**IMIPRAMINE** plus **DESIPRAMINE**), minimum level of 140 ng/mL [1001].
- 3) Hyperactivity, 10 to 54 ng/mL (**imipramine** only) [1002].
- 4) **Enuresis** in children, no correlation [1003][1004][1005].
  - a) Some studies have shown levels of 80 to 150 ng/mL (**IMIPRAMINE** plus **DESIPRAMINE**) to be effective [1006][1007].
- 5) **Ventricular premature depolarizations**, 74 to 385 ng/mL (**IMIPRAMINE** plus **desipramine**) [1008].
- 6) **Diabetic neuropathy**, less than 100 nmol/L (**IMIPRAMINE** plus **DESIPRAMINE**); 400 to 500 nmol/L required in some patients [1009].

**B) Time to Peak Concentration**

- 1) Oral: 1 hour [998].

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

- 1) Oral, tablet: 94% to 96% [1010].
  - a) The bioavailability of **IMIPRAMINE** from tablet and syrup form is equivalent (Gagnon et al, 1980).

**B) Effects of Food**

- 1) None [1011].

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

- a) 89% [1012].
  - 1) Patients with severe burns (35% to 85% BSA) exhibit increased binding during the initial convalescent phase (5 to 20 days) [1013].
  - 2) The free fraction is reduced in cancer patients [1014].
  - 3) The free fraction in rheumatoid arthritis patients is slightly lower than in healthy control subjects (9.7% vs 10.9%) [1015].

## 2J) OTHER DISTRIBUTION SITES

### aJ) Tissue

1J) At steady-state, tissue concentrations are greatest in the lung followed by the brain, the adipose tissue, and plasma [1016].

## BJ) Distribution Kinetics

### 1J) Volume of Distribution

aJ) 10 to 20 L/kg [1017][1016].

## 2.3.3J Metabolism

### AJ) Metabolism Sites and Kinetics

1J) Liver, extensive (Gram & Christensen, 1975)[1018].

aJ) First-pass metabolism occurs with extensive metabolism to conjugated and non-conjugated metabolites [1018].

bJ) N-demethylation of [imipramine](#) is under pharmacogenic control of CYP2C19 [1019].

cJ) Hydroxylation may become saturated resulting in drug accumulation [1020].

### BJ) Metabolites

1J) N-desmethyl metabolite ([DESIPRAMINE](#)), active [1021].

aJ) Patients with recurrent episodes of depression have a significantly lower [IMIPRAMINE/DESIPRAMINE](#) ratio (0.94) than those who do not experience recurrences (1.73) [1022].

bJ) [DESIPRAMINE](#) exists in a 0.3 to 15.0 ratio to [IMIPRAMINE](#) in plasma [1023].

2J) 2-hydroxy [IMIPRAMINE](#), active [1024].

aJ) Reported to depress cardiac contractility in dogs [1024].

3J) 2-hydroxydesipramine, active [1025].

aJ) Serum concentration of the hydroxy metabolites may have some relationship to the drug's toxicity (DeVane et al, 1981, DeVane & Jusko, 1981a).

## 2.3.4J Excretion

### AJ) Kidney

1J) Renal Excretion (%)

a) 0.05 to 0.1% ([DESIPRAMINE](#) only) [998].

2) [IMIPRAMINE](#) metabolites are excreted in urine [1026][1027].

### 2.3.5] Elimination Half-life

#### A) Parent Compound

##### 1) ELIMINATION HALF-LIFE

a) 6 to 18 hours [1031][1032].

1) The half-life of IMIPRAMINE in children ranges from 6 to 15 hours [1033].

2) In elderly patients the serum half-life ranges from 25 to 30 hours [1031][1034].

3) The terminal half-life of IMIPRAMINE and the active metabolites is 1.5 to 2.0 times longer following intramuscular administration than that observed following oral administration [1032].

#### B) Metabolites

1) [DESIPRAMINE](#), 12 to 36 hours [1032].

2) 2-hydroxyimipramine, 6 to 18 hours [1032].

3) 2-hydroxydesipramine, 12 to 36 hours [1032].

### 2.3.6] Extracorporeal Elimination

#### A) Hemodialysis

1) Dialyzable: No[996][1028][1029][1030]

#### B) Peritoneal

1) Dialyzable: No[996][1028][1029][1030]

## 3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

### 3.0.A] Black Box WARNING

Imipramine Hydrochloride

Oral (Tablet)

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of imipramine hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Imipramine hydrochloride is not approved for use in pediatric patients [119].

## Imipramine Pamoate

### Oral (Capsule)

#### Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of imipramine pamoate or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Imipramine pamoate is not approved for use in pediatric patients [120].

## 3.1] Contraindications

### A) Imipramine Hydrochloride

- 1) coadministration with a MAOI or use within 14 days of discontinuing a MAOI; may cause serious reactions (eg, hyperpyretic crisis, convulsive seizures, death) [119]
- 2) hypersensitivity to dibenzazepines; risk of [cross-sensitivity reactions](#) [119]
- 3) hypersensitivity to [imipramine](#) hydrochloride [119]
- 4) [myocardial infarction](#), during the acute recovery period [119]

### B) Imipramine Pamoate

- 1) coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (eg, hyperpyretic crisis, severe convulsive seizures, death) [120]



- 2)) hypersensitivity to dibenzazepines; risk of [cross-sensitivity reactions](#) [120]
- 3)) hypersensitivity to [imipramine](#) pamoate [120]
- 4)) [myocardial infarction](#), during the acute recovery period [120]

### 3.2) Precautions

#### A)) [Imipramine](#) Hydrochloride

- 1)) [suicidal ideation](#) and behavior or worsening depression, increased risk, particularly in children, adolescents, and young adults during the first few months of therapy or following changes in dosage [119]
- 2)) alcohol, excessive use; increased danger of intentional or unintentional [imipramine overdose](#) [119]
- 3)) [bipolar disorder](#), in patients at risk; increased risk of precipitation of a mixed/[manic episode](#) with only antidepressant treatment [119]
- 4)) [cardiovascular disease](#), current or history; may cause cardiac conduction defects, [arrhythmias](#), [congestive heart failure](#), [myocardial infarction](#), stroke, and [tachycardia](#) [119]
- 5)) concurrent use with [electroshock therapy](#); may increase hazards of [electroshock therapy](#) [119]
- 6)) cyclic-type psychiatric disorders, history; may cause mania or [hypomania](#) [119]
- 7)) elderly patients; increased risk of developing cardiac abnormalities [119]
- 8)) excessive exposure to sunlight; may cause [photosensitization](#) [119]
- 9)) [glaucoma](#), narrow-angle, history of; due to anticholinergic effects of [imipramine](#) hydrochloride [119]
- 10)) hepatic function, significantly impaired [119]
- 11)) [hyperthyroidism](#) or concurrent use of thyroid medications; may increase risk of cardiovascular toxicity [119]
- 12)) intraocular pressure, increased; exacerbation of condition due to cholinergic antagonism [119]
- 13)) neutrophil depression, pathological, may occur [119]
- 14)) renal function, significantly impaired [119]
- 15)) [schizophrenia](#); may activate [psychosis](#) [119]
- 16)) seizure disorder, history; may lower the convulsive threshold [119]
- 17)) surgery, elective [119]
- 18)) urinary retention, history of; due to anticholinergic effects of [imipramine](#) hydrochloride [119]

#### B)) [Imipramine](#) Pamoate

- 1)) [suicidal ideation](#) and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults during the first few months of therapy or following changes in dosage [120]
- 2)) alcohol, excessive use; increased danger of intentional or unintentional [imipramine overdose](#) [120]

- 3)) [bipolar disorder](#); increased risk of precipitation of a mixed/[manic episode](#) with only antidepressant treatment [120]
- 4)) [cardiovascular disease](#), current or history; may increase risk of [tachycardia](#), [congestive heart failure](#), cardiac conduction defects, [arrhythmias](#), [myocardial infarction](#) (MI), and [stroke](#) [120]
- 5)) concurrent use with [electroshock therapy](#); may increase hazards of [electroshock therapy](#) [120]
- 6)) elderly patients; may increase risk of ECG changes [120]
- 7)) [glaucoma](#), history of narrow-angle; exacerbation of condition due to cholinergic antagonism [120]
- 8)) [hyperthyroidism](#) or concurrent use of thyroid medications; may cause [cardiac toxicity](#) [120]
- 9)) intraocular pressure, increased; exacerbation of condition due to cholinergic antagonism [120]
- 10)) mania/[hypomania](#); risk of disease activation [120]
- 11)) [schizophrenia](#); may activate [psychosis](#) [120]
- 12)) seizure disorder, history; may lower the convulsive threshold [120]
- 13)) surgery, elective [120]
- 14)) urinary retention, history of; exacerbation of condition due to cholinergic antagonism [120]

### 3.3] Adverse Reactions

#### 3.3.1] Cardiovascular Effects

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

###### 1)) Summary

a)) Tricyclic antidepressants, including [imipramine](#) may cause [cardiac conduction disorders](#) such as [tachycardia](#), palpitations, [arrhythmias](#), and [heart block](#) [134]. Production and suppression of atrial and [ventricular arrhythmias](#) have been reported in patients receiving [imipramine](#) [129][130][135][136]. Multifocal [premature ventricular contractions](#) occurred in a 62-year-old woman following withdrawal of [imipramine](#). The depressed patient had preexisting [nonspecific intraventricular conduction delay](#) [137].

###### 2)) [Arrhythmia](#) in Adults

a)) A 25-year-old quadriplegic patient receiving oral [imipramine](#) 200 mg at bedtime developed a life-threatening [ventricular arrhythmia](#) shortly after achieving therapeutic levels [135]. This may have occurred because tetraplegic patients frequently have autonomic supersensitivity. Thus the autonomic effects of [imipramine](#) may have caused the [cardiac arrhythmia](#).

b)) A 37-year-old black male, who was receiving [antihypertensive therapy](#) ([guanethidine](#), [hydralazine](#), and [methyldopa](#)) experienced cardiac stand still and died following treatment with 25 mg of [imipramine](#) 3 times per day for 5 days, despite discontinuation of all drugs [136]. In other reports, discontinuation of [imipramine](#) usually results in improvement of [cardiac arrhythmias](#) although in some cases of [AV block](#), a pacemaker was required [138][139][140]. [Arrhythmias](#),

usually [supraventricular](#) or [ventricular tachycardia](#), have also been reported following acute [overdose of imipramine](#) [141][142].

c) The cardiovascular effects associated with [imipramine](#) therapy were evaluated in 12 men with stable [ischemic heart disease](#) who had become depressed following a [myocardial infarction](#) or [coronary artery bypass-graft surgery](#) [130]. All other drug regimens were kept constant during the course of the study. The mean maximum [imipramine](#) dose was 125 mg/day with a mean plasma level ([imipramine](#) plus desmethylimipramine) of 194 ng/mL. During the course of [imipramine](#) therapy some patients experienced an antiarrhythmic effect from the [imipramine](#), observed as a reduction in [premature ventricular contractions](#). Other cardiovascular side effects observed in this study included a modest increases in PR interval, QT interval, and heart rate, and orthostatic blood pressure changes.

d) The development of [second degree atrioventricular block](#) was significantly greater in patients with preexisting [bundle-branch block](#) than in patients with normal [electrocardiograms](#); orthostatic hypotension occurred more frequently in patients with conduction abnormalities [143].

### 3) [Arrhythmia](#) in Pediatrics

a) The cardiovascular status of 23 pediatric patients (ages 5 to 17 years), who were candidates for [imipramine](#) therapy (eg, oppositional behavior, conduct disorders, and depression), were evaluated before and after the initiation of [imipramine](#) therapy. Each patient was started on 1.5 mg/kg/day which could be increased to a maximum of 5 mg/kg/day, given in three divided doses. The follow-up cardiovascular evaluation was conducted 10 to 14 days after clinical improvement in their condition or steady-state serum concentration of between 150 nanograms (ng)/mL and 250 ng/mL. Resting heart rate increased and the PR interval lengthened (average 21.2 msec) in all 23 children (p less than 0.001). One child developed Mobitz type II block while on [imipramine](#), but this child had a resting PR interval of 176 msec before the initiation of [imipramine](#) therapy. Based on these findings the authors support the recommendation that baseline [electrocardiogram](#) should be considered in all patients. In addition, patients with a family history of sudden death, a baseline PR interval greater than the 90th percentile for age, or any alterations in intraventricular conduction are candidates for ambulatory [Holter monitor](#) when starting [imipramine](#) therapy [144].

#### 3.3.1.B) [Cardiogenic shock](#)

1) An imipramine-provoked paradoxical [pheochromocytoma](#) crisis occurred in a 35-year-old male who presented to the hospital with severe [cardiogenic shock](#) after taking two unknown doses of [imipramine](#) for headaches. The hypotension was unresponsive to fluids and anotropes [145]. Subsequent [CT scan](#) revealed a [pheochromocytoma](#), which was confirmed with other diagnostic tests. Previous cases reports of the adverse effects of [imipramine](#) in patients with [pheochromocytoma](#) have resulted in hypertensive crises. It appears that [imipramine](#) should be avoided or used with caution in patients with known or suspected [pheochromocytoma](#).

2) [Cardiogenic shock](#), vasoconstriction, [vasospasm](#) of the hands and feet ([acrocyanosis](#)), and [myocarditis](#) have each been reported in 1 to 2 patients on [imipramine](#) therapy [146][147][145][148].

#### 3.3.1.C) [Cardiomyopathy](#)

1) [Congestive cardiomyopathy](#) was reported in a 50-year-old male after receiving tricyclic antidepressants for a 5 year period ([amitriptyline/perphenazine](#) for 6 months, then [imipramine](#) 150 mg/day for 4 years). The patient experienced gradual onset of weakness, shortness of breath, and pedal edema over 2 months prior to admission. Evaluation revealed cardiomegaly and [interstitial edema](#) on [chest x-ray](#) and EKG revealed bilateral enlargement. The patient improved somewhat with [digoxin](#), [furosemide](#) and [hydralazine](#)

but remained severely disabled (functional class 3) [149]. A cause-effect relationship was not definitely established in this case.

### 3.3.1.D] Dead - sudden death

1) According to one study, the use of higher-dose tricyclic antidepressants (TCAs) was associated with an increased risk of sudden cardiac death, while lower doses did not increase this risk. In a cohort study including 481,744 persons and 1487 cases of sudden cardiac death occurring in a community setting, researchers found that compared to nonuse, the current use of TCAs was associated with a dose-related increase in the risk of sudden cardiac death. For doses lower than 100 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) [157].

2) An 8-year-old boy died of [cardiac arrest](#) that was attributed to [imipramine](#) toxicity. Although there were no signs that he had taken more than the prescribed dose, the dose at time of death (6.9 milligrams/kilogram/day (mg/kg/day)) was somewhat in excess of the recommended dose of 5 mg/kg/day. One month after his dose had been raised to 100 mg twice per day (approximately a year after starting treatment), he complained of his heart hurting and of being dizzy. Two months later, [dextroamphetamine](#) 5 mg/day was added to his regimen and was raised to 10 mg/day one month later. Two months after the initial cardiac episode, he again complained of his heart hurting. One month later, while playing basketball, he died of [cardiac arrest](#). On autopsy (20 hours after death), highly elevated venous and ventricular levels of [imipramine](#) and its metabolite, [desipramine](#), were the only abnormalities found [158].

### 3.3.1.E] Electrocardiogram abnormal

#### 1) Summary

a) ECG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval, and flattened T waves [129].

2) In one comparative study, [phenelzine](#) and mianserin were less likely than [imipramine](#) or [amitriptyline](#) to produce changes in cardiac conduction, in patients without cardiac disease. Prolongation of the PR interval was observed with [imipramine](#) and [amitriptyline](#) but not with [phenelzine](#) or mianserin. There was a trend towards prolongation of the QRS complex with the tricyclics, as well as the QT interval; no QRS changes were observed with [phenelzine](#) or mianserin and there was a trend for [phenelzine](#) to decrease the QT interval, whereas mianserin produced no effect on the QTc interval. These data suggest that mianserin and [phenelzine](#) are less likely than [imipramine](#) or [amitriptyline](#) to produce [heart block](#) in patients with cardiac disease; mianserin appeared to be the least likely of the four agents to induce cardiac conduction abnormalities [128].

3) Forty-four depressed patients receiving [imipramine](#) 3.5 mg/kg/day for 4 weeks demonstrated prolonged PR, QRS, and QTc intervals, lowered T-wave amplitude, and increased heart rate compared to a 2 week drug-free period. None of these patients developed severe intraventricular conduction abnormalities nor high-grade [AV block](#) [131].

4) [Imipramine](#) therapy in the elderly has been associated with increased heart rate and isolated ECG complications (shortening of the QT interval, changes in ST segments, and T waves) [132]. Two elderly, depressed patients, with preexisting [cardiac arrhythmias](#), had significant increases in PR interval, QRS

segment, and QT interval following treatment with oral [imipramine](#) 3.5 mg/kg/day. Both patients also had a reduction in atrial and [ventricular premature depolarizations](#) during therapy [133].

### 3.3.1.F] [Heart block](#)

1) The development of [second degree atrioventricular block](#) was significantly greater in patients with preexisting [bundle-branch block](#) than in patients with normal [electrocardiograms](#); orthostatic hypotension occurred more frequently in patients with conduction abnormalities [143].

### 3.3.1.G] [Heart failure](#)

1) Tricyclic antidepressants, including [imipramine](#), may precipitate [heart failure](#) [123][124].

### 3.3.1.H] [Hypertension](#)

1) A 57-year-old female treated with 150 mg/day of [imipramine](#) for 12 days developed [hypertension](#) [150]. Blood pressure before therapy was noted to be 140/90 mmHg and 3 days after initiating [imipramine](#) for [endogenous depression](#), the blood pressure rose to 150/110 mmHg. Nine days after initiating therapy the blood pressure had risen to 175/120 mmHg with no associated changes in the EKG. Twenty-four hour urinary excretion of noradrenaline-adrenaline and vanillylmandelic acid was normal. Dosage reduction failed to lower blood pressure and so the drug was discontinued. After 3 weeks the blood pressure was close to or at controlled levels.

2) [Imipramine](#), 75 mg at bedtime, produced a rise in diastolic blood pressure in 18 enuretic boys (mean age 9.8 years). Supine diastolic pressure increased by 8 +/- 6 mmHg and standing by 10 +/- 12 mmHg [151].

### 3.3.1.I] [Hypotension](#)

#### 1) Summary

a) Orthostatic hypotension has been reported in patients receiving [imipramine](#) [152][153][154]. Elderly depressed patients (n=45) may be at an increased risk for orthostatic hypotension if they have preexisting severe [heart disease](#), impaired left ventricular function, or are taking concurrent cardiovascular medications. Another factor, that requires further assessment, was increased forearm resistance. Individuals with increased forearm resistance had a greater frequency of imipramine-induced orthostatic hypotension than those with normal or low forearm resistance. Patients were receiving therapeutic doses of [imipramine](#) [152].

2) A 9-year-old white female treated with [imipramine](#) 25 mg twice daily for 9 days developed postural hypotension. On the fifth day of therapy, the child developed decreased appetite, dry mouth, and constipation. During the sixth to ninth day of therapy, she developed weakness, and dizziness upon standing, pallor, diaphoresis, vomiting when propped up, and a rapid heart rate. Physical exam revealed a supine pulse rate of 120 beats/min with supine blood pressure of 100/70 mmHg. Sitting blood pressure was noted to fall to 80/50 mmHg and [pulse rate increased](#) to 170 beats /min, and the patient also became nauseated and sweated profusely. Upon standing, blood pressure dropped to 60/0 mmHg with pulse increasing to greater than 220 beats/min in association with a syncopal attack. An ECG revealed a [first degree AV block](#). Discontinuation of [imipramine](#) resulted in improvement of the patient's condition over the 7 day hospital course with subsequent normalization of ECG [153].

3) A study of 44 depressed adults receiving therapeutic doses of [imipramine](#) (average 245 mg/day in males, 218 mg/day in females) demonstrated a significant decrease in blood pressure upon standing; average decrease during [imipramine](#) therapy was 26.1 mmHg during therapy and 10.9 mmHg prior to therapy. This decrease was independent of age, plasma level or preexisting heart rate [154].

4) Forty-five elderly patients (mean age 63.6) were initially treated with 25 mg/day [imipramine](#) with dose being increased to 150 mg/day [155]. Cardiovascular function was assessed 3 times during the course of the

study (pretreatment, day 7 and day 28). On day 7 and day 28 the patient exhibited a significant orthostatic change in diastolic blood pressure and increase in heart rate compared to pretreatment.

5J) The cardiovascular effects of [imipramine](#), [doxepin](#), and placebo were compared in 24 depressed patients with [heart disease](#). The tricyclic antidepressants had no effects on left ventricular ejection fraction but did cause orthostatic changes in blood pressure. The [imipramine](#) therapy was associated with a reduction in [premature ventricular contractions](#), which was not consistently seen in the placebo and [doxepin](#) treated patients. Based on the results of this study it would appear that depressed patients with preexisting [heart disease](#), without any severe impairment of myocardial performance, can be treated with [imipramine](#) or [doxepin](#) without an adverse effect on [ventricular rhythm](#) or hemodynamic function [156].

### 3.3.1.J] Myocarditis

1J) A 54-year-old female developed [myocarditis](#) and [hepatitis](#) after restarting [imipramine](#) therapy. The patient died three weeks later secondary to the [myocarditis](#). It could not be determined if this rare [hypersensitivity reaction](#) was directly related to the [imipramine](#), its [desipramine](#) metabolite, or the combination of [imipramine](#) and [desipramine](#) [148].

### 3.3.1.K] Prolonged QT interval

1J) In one comparative study, [phenelzine](#) and mianserin were less likely than [imipramine](#) or [amitriptyline](#) to produce changes in cardiac conduction, in patients without cardiac disease. Prolongation of the PR interval was observed with [imipramine](#) and [amitriptyline](#) but not with [phenelzine](#) or mianserin. There was a trend towards prolongation of the QRS complex with the tricyclics, as well as the QT interval; no QRS changes were observed with [phenelzine](#) or mianserin and there was a trend for [phenelzine](#) to decrease the QT interval, whereas mianserin produced no effect on the QTc interval. These data suggest that mianserin and [phenelzine](#) are less likely than [imipramine](#) or [amitriptyline](#) to produce [heart block](#) in patients with cardiac disease; mianserin appeared to be the least likely of the four agents to induce cardiac conduction abnormalities [128].

2J) ECG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval, and flattened T waves [129].

3J) The cardiovascular effects associated with [imipramine](#) therapy were evaluated in 12 men with stable [ischemic heart disease](#) who had become depressed following a [myocardial infarction](#) or [coronary artery bypass-graft surgery](#) [130]. All other drug regimens were kept constant during the course of the study. The mean maximum [imipramine](#) dose was 125 mg/day with a mean plasma level ([imipramine](#) plus desmethylinipramine) of 194 ng/mL. During the course of [imipramine](#) therapy some patients experienced an antiarrhythmic effect from the [imipramine](#), observed as a reduction in [premature ventricular contractions](#). Other cardiovascular side effects observed in this study included a modest increases in PR interval, QT interval, and heart rate, and orthostatic blood pressure changes.

4J) Forty-four depressed patients receiving [imipramine](#) 3.5 mg/kg/day for 4 weeks demonstrated prolonged PR, QRS, and QTc intervals, lowered T-wave amplitude, and increased heart rate compared to a 2 week drug-free period. None of these patients developed severe intraventricular conduction abnormalities nor high-grade [AV block](#) [131].

5J) [Imipramine](#) therapy in the elderly has been associated with increased heart rate and isolated ECG complications (shortening of the QT interval, changes in ST segments, and T waves) [132]. Two elderly, depressed patients, with preexisting [cardiac arrhythmias](#), had significant increases in PR interval, QRS segment, and QT interval following treatment with oral [imipramine](#) 3.5 mg/kg/day. Both patients also had a reduction in atrial and [ventricular premature depolarizations](#) during therapy [133].

### 3.3.1.L] Summary



1J) The following cardiovascular adverse effects may occur with tricyclic antidepressants, including imipramine: myocardial infarction, stroke, heart block, precipitation of congestive heart failure, ECG changes, orthostatic hypotension, hypertension, and tachycardia [123][124]. ECG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval, and flattened T waves [129]. Cardiogenic shock, vasoconstriction, vasospasm of the hands and feet (acrocyanosis), and myocarditis have each been reported in 1 to 2 patients on imipramine therapy [146][147][145][148]. Two authors reported that tricyclic antidepressants, when given in therapeutic doses, are essentially free of adverse cardiovascular effects in patients without cardiovascular disease and may improve the status of patients with ventricular arrhythmias [159][143].

### 3.3.1.MJ Vasoconstriction

1J) A 37-year-old female, developed severe and prolonged episodes of vasospasm of the hands within 10 days of the discontinuation of her amitriptyline therapy and the initiation of 150 mg/day imipramine. Vasospasm reoccurred upon rechallenge [146].

2J) Acrocyanosis of the hands and feet occurred in an 11-year-old girl following imipramine therapy (25 mg at bedtime for approximately 10 weeks) for nocturnal enuresis [147]. The patient developed initial symptoms 3 weeks after initiation of treatment (painful swelling of metacarpophalangeal joints of the feet). Examination after 10 weeks of treatment revealed cold, blue and moist hands and feet which blanched on pressure. Livedo reticularis was observed on the forearms. Withdrawal of imipramine resulted in resolution of symptoms in 3 days.

### 3.3.2J Dermatologic Effects

#### 3.3.2.AJ Discoloration of skin

1J) Hyperpigmentation was described in 4 women (53 to 75 years old) receiving imipramine 150 to 375 mg for 4 to 15 years [192]. Hyperpigmentation began after 2 to 11 years of use. Coloration was described as slate-gray in 2 women and as dark brown or golden brown in the other 2. The site of the reaction was in the face, chest, arms, and hands. One woman also had a darkening of her iris. The pigmentation disappeared over 6 to 12 months in 2 of the women who agreed to discontinue imipramine.

2J) A 46-year-old male was treated with imipramine 75 to 100 mg three times/day for 9 years and developed purple pigmentation of his face, neck, and fingers [193]. Characteristically the skin of the nose and ears was unaffected, and the patient had normal skin folds with no ophthalmological disturbances.

3J) A 48-year-old white female developed a slate-gray discoloration in sun-exposed areas, predominately her face, dorsa of both hands, and eyes, after receiving imipramine 150 mg/day for five years [194]. These discolored areas became lighter after discontinuation of the imipramine therapy and returned to normal within one year.

#### 3.3.2.BJ Flushing

1J) Tricyclic antidepressants, including imipramine, may cause flushing [123][124].

#### 3.3.2.CJ Photosensitivity

1J) Tricyclic antidepressants, including imipramine, have caused photosensitivity. Patients should avoid excessive exposure to sunlight [123][124].

#### 3.3.2.DJ Rash

1J) Tricyclic antidepressants, including imipramine, may cause skin rash, urticaria and itching [123][124].

### 3.3.3] Endocrine/Metabolic Effects

#### 3.3.3.A] Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- [ACUTE PORPHYRIAS](#)

#### 3.3.3.B] Body weight problem

1) Tricyclic antidepressants, including [imipramine](#), may cause weight gain or weight loss [123][124].

#### 3.3.3.C] Disorder of glucose regulation

1) Tricyclic antidepressants, including [imipramine](#), may cause elevation or depression of blood glucose levels [123][124].

#### 3.3.3.D] Galactorrhea

1) Tricyclic antidepressants, including [imipramine](#), may cause [galactorrhea](#) in females [123][124].

2) A 34-year-old female treated with [imipramine](#) 75 to 100 mg/day for 6 months developed spontaneous [galactorrhea](#). Discontinuation of [imipramine](#) resulted in subsiding of the lactation which recurred when therapy with [imipramine](#) was resumed. During [imipramine](#) therapy, it was noted that the patient had low levels of serum serotonin and urinary gonadotropins. The author postulated that the mechanism for the [galactorrhea](#) was similar to that seen with [reserpine](#) which involves inhibition of the normal hypothalamic inhibition of pituitary prolactin secretion [175].

#### 3.3.3.E] Gynecomastia

1) Tricyclic antidepressants, including [imipramine](#), may cause [gynecomastia](#) in males [123][124].

#### 3.3.3.F] Hyperthyroidism

1) A case of a 9.5-year-old female was treated with 25 mg/day oral [imipramine](#) for [enuresis](#) and also received desiccated thyroid therapy; the patient demonstrated increased restlessness, hyperkineticism, nervousness, easy fatigability, fine tremors and warm skin. Physical exam revealed a resting heart rate of 120 beats/min with deep tendon reflexes noted to be 4 plus without clonus. Lab values revealed a thyroxine level of 9.2 mg/dL and a triiodothyronine uptake of 31.9%. EKG demonstrated [sinus tachycardia](#) with ST-T wave changes and basal metabolic rate was elevated by 33%. Discontinuing [imipramine](#) but continuing the same dose of thyroid resulted in the child becoming euthyroid [174].

#### 3.3.3.G] Hypoglycemia

1) A 50-year-old male treated with 200 mg/d of [imipramine](#) developed severe [hypoglycemia](#) [178]. Six days after starting [imipramine](#) therapy the patient complained of fatigue, dizziness, loss of weight, and increased appetite. On laboratory examination, he was found to have a nonfasting serum glucose of 57 mg/dL with all other lab values within normal limits. [Imipramine](#) therapy was discontinued and his serum glucose returned to 79 mg/dL and symptoms disappeared. Following an unintentional rechallenge the man began complaining of weakness and dizziness one week later. At that time his serum glucose was 34 mg/dL. Following discontinuation of the [imipramine](#) therapy his serum glucose returned to normal.

2) [Imipramine](#) may increase an individual's sensitivity to insulin-induced [hypoglycemia](#), but does not affect the counter-regulatory response of [ACTH](#) and cortisol [179].

#### 3.3.3.H] Large breast



1J) Tricyclic antidepressants, including [imipramine](#), may cause [breast enlargement](#) not associated with gravidity in females [123][124].

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

1J) Tricyclic antidepressants, including [imipramine](#), may cause syndrome of [inappropriate antidiuretic hormone secretion](#) [123][124].

2J) [Imipramine](#) was associated with SIADH in a 78-year-old woman during therapy for [major depression](#). The patient received [imipramine](#) 25 to 50 mg orally daily for approximately 3 months prior to admission. [Hyponatremia](#) was observed upon admission and subsided during a 9 day interval without [imipramine](#) therapy. The patient subsequently developed SIADH with [bupropion](#) and upon rechallenge with [imipramine](#) [176].

3J) A 73-year-old thin and frail white female was admitted to a psychiatric unit for evaluation after deliberate ingestion of denture cleaning fluid [177]. She was diagnosed with severe depression and started on [paroxetine](#) therapy. Two weeks later the [paroxetine](#) was discontinued because the depression was getting worse. A single session of [electroconvulsive therapy](#) was tried and then she was started on [imipramine](#) syrup, 25 mg twice daily. The dose was increased to 125 mg per day, given in divided doses, and [diazepam](#) was used in doses up to 10 mg/day to control her agitation. Over the next few weeks her mental condition improved, but she did fall and sustained a fractured left femur neck. Her mental condition continued to improve, but her mobility deteriorated and she suffered several more falls. Physical examination revealed a profound orthostatic drop in blood pressure (40 mmHg) and she had [hyponatremia](#) (124 mmol/l) and a low serum osmolality (266 mOsm/kg). Water intoxication was ruled out and a diagnosis of [inappropriate secretion of antidiuretic hormone](#) was made. The [imipramine](#) therapy was then held. Over the next ten days her serum sodium levels returned to the normal range.

### 3.3.4] Gastrointestinal Effects

#### 3.3.4.A] [Black hairy tongue](#)

1J) Tricyclic antidepressants, including [imipramine](#), may cause black tongue[123][124].

#### 3.3.4.B] [Colitis](#)

1J) [Ischemic colitis](#), requiring surgical intervention, has been reported in one patient following the ingestion of a large quantity of [imipramine](#) [184]. The individual was a 38-year-old female with a past medical history of depression, hospitalized following an ingestion of unspecified quantity of [imipramine](#). Her serum [imipramine](#) level was 1,092 micrograms/milliliter. Over the next few days her abdomen became increasingly distended with rebound tenderness and absence of bowel sounds. [Laparotomy](#) revealed a necrotic ascending and transverse colon which was subsequently removed and the patient's condition improved.

#### 3.3.4.C] [Constipation](#)

1J) Tricyclic antidepressants have been known to cause constipation. Because [imipramine](#) is a tricyclic antidepressant, constipation may occur with this drug [123][124].

#### 3.3.4.D] [Diarrhea](#)

1J) Tricyclic antidepressants, including [imipramine](#), may cause diarrhea [123][124].

#### 3.3.4.E] [Epigastric pain](#)

1J) Tricyclic antidepressants, including [imipramine](#), may cause epigastric distress [123][124].

**3.3.4.F] Loss of appetite**

1) Tricyclic antidepressants have been known to cause anorexia. Because [imipramine](#) is a tricyclic antidepressant, anorexia may occur with this drug [123][124].

**3.3.4.G] Nausea and vomiting**

1) Tricyclic antidepressants have been known to cause nausea and vomiting. Because [imipramine](#) is a tricyclic antidepressant, nausea and vomiting may occur with this drug. Nausea may also occur due to a withdrawal reaction after abrupt cessation of chronic [imipramine](#) therapy [123][124].

**3.3.4.H] Paralytic ileus**

1) Tricyclic antidepressants, including [imipramine](#), may cause [paralytic ileus](#) [123][124].

**3.3.4.I] Parotid swelling**

1) Tricyclic antidepressants, including [imipramine](#), may cause parotid swelling[123][124].

**3.3.4.J] Stomatitis**

1) Tricyclic antidepressants have been known to cause [stomatitis](#). Because [imipramine](#) is a tricyclic antidepressant, [stomatitis](#) may occur with this drug [123][124].

**3.3.4.K] Xerostomia**

1) [Xerostomia](#) is frequently associated with [imipramine](#) therapy in usual therapeutic doses (150 mg/day). [Xerostomia](#) or dry mouth is often associated with gum shrinkage, inflammation of the oral cavity, [stomatitis](#), cracking of the lips and corners of the mouth, [pseudomembrane formation](#), [hairy tongue](#) with white or black or bald beefy red tongue, ill-fitting dentures, tooth loss, and [oral moniliasis](#). Discontinuation of the drug and/or treatment with [pilocarpine](#) (5 mg four times/day) usually results in an increase of salivation [180][181].

2) [Imipramine](#), 75 mg every day, given to 12 volunteers in a placebo controlled study caused a significant reduction in salivary secretion rate [182].

3) A comparison of 5 different antidepressants on salivary flow reveals that [amitriptyline](#) and [doxepin](#) had the greatest effect on salivation and [desipramine](#) the least [183]. [Imipramine](#) and [nortriptyline](#) were intermediate and interchangeable in their effects.

**3.3.5] Hematologic Effects****3.3.5.A] Agranulocytosis**

1) Imipramine-induced [agranulocytosis](#) is rare [122]. During [imipramine](#) therapy, [leukocyte](#) and differential blood counts are recommended if symptoms of fever and sore throat develop. In the event of pathological neutrophil depression, [imipramine](#) should be discontinued [123][124].

2) A 59-year-old white female treated with [imipramine](#) 50 mg three times per day for 2 months developed [agranulocytosis](#) which was fatal. The patient died 2 weeks after discontinuing [imipramine](#) [125].

**3.3.5.B] Bone marrow depression**

1) [Bone marrow depression](#), including [agranulocytosis](#), [eosinophilia](#), [purpura](#), and [thrombocytopenia](#), has been reported in patients treated with [imipramine](#) or other tricyclic antidepressants in clinical trials [126]. During [imipramine](#) therapy, [leukocyte](#) and differential blood counts are recommended if symptoms

of fever and sore throat develop. In the event of pathological neutrophil depression, [imipramine](#) should be discontinued [123][124].

### 3.3.5.C] Eosinophilia

1J) A 55-year-old male treated with [imipramine](#) 25 mg/day developed asymptomatic [eosinophilia](#). The patient's WBC count was noted to be 19,650 which gradually decreased in association with an eosinophil count of 693 (normal range, 50 to 300). All through the course, the patient remained asymptomatic and well. Following discontinuation of the drug, the patient recovered with the [eosinophilia](#) subsiding [127].

### 3.3.5.D] Immune thrombocytopenia

1J) [Immune thrombocytopenia](#) was reported in a 5-year-old boy following [imipramine](#) administration. The child, who was initiated on [imipramine](#) 10 mg/day for ADHD, was healthy with normal development and an unremarkable medical history. A few weeks earlier, his cell counts were within normal limits with a normal [platelet](#) count (288,000/mcL). One week after [imipramine](#) was started, he was admitted to a pediatric neurology department with a language impairment. Lab findings included [hemoglobin](#) 13.1 g/dL, [platelets](#) 18,000/mcL, [reticulocyte](#) count 1%, and WBC count 11,400/mcL, neutrophils 70%, and [lymphocytes](#) 30%. There was no evidence of [hemolytic anemia](#). Direct and [indirect antiglobulin tests](#) were positive (+3 and +1, respectively). Subsequently, [imipramine](#) was withdrawn and the patient was started on a 5-week course of [methylprednisolone](#) (30 mg/kg/day for 3 days, 20 mg/kg/day for 4 days, 10 mg/kg/day for 7 days, 5 mg/kg/day for 7 days, and 1 mg/kg/day for 15 days). During [methylprednisolone](#) therapy, [platelet](#) counts were between 225,000 and 461,000 cells/mcL; on day 7, the [platelet](#) count was 391,000 cells/mcL. Indirect and [direct antiglobulin tests](#) were negative at 5 weeks and 4 months following [methylprednisolone](#) initiation, respectively. The patient did not develop [thrombocytopenia](#) again over the next 7 months of outpatient follow-up [121].

## 3.3.6] Hepatic Effects

### 3.3.6.A] Fulminant hepatic failure

1J) A 11-year-old boy developed [fulminant hepatic failure](#) seven days after being started on [imipramine](#) 25 mg at bedtime for [enuresis](#) [190]. Histologically, the liver showed massive hepatocellular necrosis with [bile duct proliferation](#) and loss of parenchymal volume. Mild amounts of [acute and chronic inflammation](#) were found in the portal areas. Hepatocellular necrosis occurred predominantly in the pericentral areas with focal hemorrhage encircling the central veins. The damage was so extensive a liver transplant was required.

### 3.3.6.B] Hepatitis

1J) A rare [hypersensitivity reaction](#) to [imipramine](#) or [desipramine](#) was associated with the development of [hepatitis](#) and [myocarditis](#)[148].

### 3.3.6.C] Hepatotoxicity

1J) Although an infrequent occurrence, the mechanism by which [hepatotoxicity](#) induced by [imipramine](#) ([hepatic necrosis](#)) occurs is unknown, but may be a [hypersensitivity reaction](#). Elevations in [bilirubin](#), [alkaline phosphatase](#), transaminases, and other liver function tests can occur within one to two weeks of the start of therapy. Clinical symptoms include [pruritus](#), [jaundice](#), icterus, rashes (erythematous maculopapular, desquamation, [xanthelasma](#) and xanthomata), and splenomegaly. Most cases improve following discontinuation of therapy. However, a few patients conditions were so severe that they either died or required a liver transplant [186][187][188][189][148][190].

### 3.3.6.D] Increased liver enzymes

1) High, single-daily dosing of [imipramine](#) may be more hazardous to the liver than divided doses. A 33-year-old female was receiving 300 mg (6 mg/kg) of [imipramine](#) at bedtime along with [thiothixene](#) 10 mg and developed an elevation in liver enzymes [189]. Prior to the hospitalization for worsening mental status she had been receiving 200 to 300 mg/d of [imipramine](#) in divided doses. On day 26 of the single daily dosage of [imipramine](#) therapy, liver function tests were ordered following subjective complaints by the patient. The test revealed an elevation in liver enzymes. No baseline liver function tests were obtained at the time of hospitalization, but a previous liver function test taken one month after the initiation of [imipramine](#) therapy was normal. Antihepatitis A and B antibodies and HAA tests were negative. The [imipramine](#) therapy was discontinued and the [thiothixene](#) therapy was continued. Two weeks following the discontinuation of the [imipramine](#) therapy liver function returned to normal.

### 3.3.6.E] Jaundice

1) [Jaundice](#), possibly presenting as [obstructive jaundice](#), has occurred with tricyclic antidepressant therapy and may occur with [imipramine](#) therapy [123][124].

### 3.3.6.F] Summary

1) [Hepatotoxicity](#) induced by [imipramine](#) ([hepatic necrosis](#)) occurs infrequently. The mechanism by which this adverse reaction occurs is unknown, but may be a [hypersensitivity reaction](#). Elevations in [bilirubin](#), [alkaline phosphatase](#), transaminases, and other liver function tests can occur within one to two weeks of the start of therapy. Clinical symptoms include [pruritus](#), [jaundice](#), icterus, rashes (erythematous maculopapular, desquamation, [xanthelasma](#) and xanthomata), and splenomegaly. Most cases improve following discontinuation of therapy. However, a few patients conditions were so severe that they either died or required a liver transplant [186][187][188][189][148][190].

## 3.3.7] Immunologic Effects

### 3.3.7.A] Cross sensitivity reaction

1) [Imipramine](#) may exhibit cross-reactivity with [desipramine](#) [123][124]  
 2) Two patients developed a skin rash during therapy with [desipramine](#) ([Norpramin\(R\)](#)) and [amitriptyline](#) ([Elavil\(R\)](#)) [197]. Discontinuation of these medications in each patient resulted in subsidence of the skin rash. [Doxepin](#) was substituted in the patient receiving [desipramine](#) and [imipramine](#) was substituted in the patient receiving [amitriptyline](#). On both occasions, recurrence of the rash did not occur. These data would suggest that substitution of a structurally dissimilar antidepressant agent is a viable alternative in patients developing allergic skin reactions.

### 3.3.7.B] Immune hypersensitivity reaction

1) Tricyclic antidepressants, including [imipramine](#), may cause an [allergic reaction](#). Symptoms may include skin rash, itching, [petechiae](#), and edema that is generalized and/or localized to the face or tongue [123][124]  
 2) Although an infrequent occurrence, the mechanism by which [hepatotoxicity](#) induced by [imipramine](#) ([hepatic necrosis](#)) occurs is unknown, but may be a [hypersensitivity reaction](#). Elevations in [bilirubin](#), [alkaline phosphatase](#), transaminases, and other liver function tests can occur within one to two weeks of the start of therapy. Clinical symptoms include [pruritus](#), [jaundice](#), icterus, rashes (erythematous maculopapular, desquamation, [xanthelasma](#) and xanthomata), and splenomegaly. Most cases improve following discontinuation of therapy. However, a few patients conditions were so severe that they either died or required a liver transplant [186][187][188][189][148][190].

3J) A rare hypersensitivity reaction to imipramine or desipramine was associated with the development of hepatitis and myocarditis[148].

### 3.3.8] Musculoskeletal Effects

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

1J) 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, doxepine, 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 [195].

#### 3.3.8.B] Hip fracture

1J) An increased incidence of hip fracture was reported in elderly patients receiving psychotropic agents. This study was a case-control evaluation of 1021 patients with hip fractures and 5606 control patients. An increased risk of hip fracture was observed with the use of hypnotic/anxiolytic agents with a long elimination half-life (greater than 24 hours), tricyclic antidepressants, and antipsychotic agents. Current users were defined as subjects who had received a prescription in the 30 day period prior to the admission date for the initial hospitalization. The long half-life hypnotic/anxiolytic agents studied were lorazepam, diazepam, chlorthalidone, and barbiturates (excluding phenobarbital). The tricyclic antidepressants included amitriptyline, doxepin, and imipramine; antipsychotic agents evaluated were thioridazine, haloperidol, chlorpromazine, and perphenazine/amitriptyline. In contrast, shorter-acting hypnotic/anxiolytic agents (half-life of 24 hours or less) were not associated with an increased risk of hip fracture in these patients. The most frequently used agents in this category were diphenhydramine, hydroxyzine, and chloral hydrate. The increased risk of hip fracture observed in this study was directly related to the doses of the drugs. Analysis for confounding by dementia did not alter the results. Additional studies are needed to confirm these results in this and other populations and to evaluate the effects of other psychotropic drugs that have less pronounced sedative effects [196].

#### 3.3.8.C] Myasthenia gravis

See Drug Consult reference: DRUG-INDUCED MYASTHENIA GRAVIS

### 3.3.9] Neurologic Effects

#### 3.3.9.A] Akathisia

1J) One patient developed akathisia while receiving imipramine therapy and 4 others developed the same while receiving desipramine, trazodone, or tranlycypromine. The imipramine patient was a 54-year-old female who was treated with alprazolam and imipramine for depression. After titrating the dose of imipramine to 150 mg/day, the patient complained of an uncomfortable feeling in her legs and the inability to remain still. Propranolol 10 mg three times daily was started, and the symptoms remitted completely within several hours of the first dose. Discontinuation of the propranolol resulted in a recurrence of the akathisia within 24 hours [171].

**3.3.9.B] Asthenia**

1J) Tricyclic antidepressants, including [imipramine](#), may cause weakness [123][124].

**3.3.9.C] Cerebral ischemia**

1J) A 59-year-old male treated with usual therapeutic doses of [imipramine](#) for mild depression developed cerebral ischemic attacks [160]. Two weeks after starting drug therapy paresthesia over the entire left side of his body was noted with short attacks of [speech disturbances](#). The drug was discontinued but paresis continued to progress with total involvement and total stenosis of the medial cerebral artery. Although no definite cause and effect relationship was established, the author postulated that tricyclic antidepressants may cause recurrent ischemic attacks in persons with partial obstruction of the cerebral arteries.

**3.3.9.D] Confusion**

1J) A high number of geriatric patients on tricyclic antidepressant therapy have developed confusional reactions characterized as restlessness, sleep disturbances, forgetfulness, agitation, disorientation, and delusions. This reaction does not appear to be dose-related and is possibly due to the central anticholinergic effects of these drugs. These episodes have been reported to develop within the first 2 weeks of drug therapy and are usually self-limiting, lasting from 3 to 20 days. However, reduction of dosage or discontinuation of the drug appears to result in resolution of these confusional reactions more quickly [112].

**3.3.9.E] Dizziness**

1J) Tricyclic antidepressants, including [imipramine](#), may cause dizziness and proneness to falling [123][124].

**3.3.9.F] Gilles de la Tourette's syndrome**

1J) Two children experienced tics or [Tourette's syndrome](#) that may have been precipitated by [imipramine](#) [172]. Motor (throat clearing, head shaking) and vocal tics ([stuttering](#), [echolalia](#), palilalia, profane utterances) developed in the boys two weeks after treatment with [imipramine](#) (75 to 100 mg/day) for ADHD and concurrent depression. The tics remained despite discontinuation of the [imipramine](#). Remission of the tics was accomplished through the use of [haloperidol](#) and [thioridazine](#).

**3.3.9.G] Headache**

1J) Tricyclic antidepressants, including [imipramine](#), may cause headache. Headache may also occur due to a withdrawal reaction after abrupt cessation of chronic [imipramine](#) therapy [123][124].

**3.3.9.H] Impaired psychomotor performance**

1J) A placebo-controlled study of healthy male volunteers demonstrated deterioration of driving skills in 10 who received 25 mg [imipramine](#) three times a day compared with 10 who received placebo and 10 who were controls [167].

**3.3.9.I] Myoclonus**

1J) A high incidence of myoclonus was reported during cyclic antidepressant therapy with [imipramine](#), [desipramine](#), [amitriptyline](#), [doxepin](#), [trazodone](#), [nortriptyline](#), and [maprotiline](#) [170]. Ninety-eight patients with [major depression](#) (93) or [panic disorder](#) were treated with these agents in initial doses of 50 mg daily of [imipramine](#) or its equivalent, increasing to a maximum of 300 mg daily after several weeks. Of these patients, 39 (40%) developed myoclonus after initiation of therapy, with the myoclonus being clinically significant in 9 (9%) and resulting in withdrawal of the antidepressant or a medication change.



Myoclonus occurred within one month of initiation of therapy in 81% of the 39 patients, with 46% of patients developing myoclonus within 2 weeks; the mean dose of antidepressant administered at the time of myoclonus was 169 mg daily in [imipramine](#) equivalents, which was similar to the mean dose utilized by the patients not developing myoclonus (164 mg daily). Myoclonus was reversible upon withdrawal of the antidepressant but persisted if medication changes were not initiated; however, spontaneous remission of myoclonus was observed in 9 patients. No predictors for the development of myoclonus were observed.

### 3.3.9.J] Seizure

1) [Imipramine](#) has been shown to decrease the convulsive threshold [161] and has been documented to cause seizure disorders including the occurrence of grand mal tonic-clonic seizures in patients with or without seizure histories. Three reports have cited cases in pediatric patients [162][163][164]. However, cases of grand mal seizures occurring in younger adults (30 years old) have also been reported [162][165]. Discontinuation of the tricyclic antidepressant and/or institution of [anticonvulsant therapy](#) usually results in control of seizures.

2) A 25-year-old female that had been treated with 4 weeks therapy of [imipramine](#) (150 mg/day) and [clorazepate](#) (40 mg/day) developed a seizure following the abrupt discontinuation of [clorazepate](#) therapy [166]. Since the seizure could not be solely contributed to the abrupt discontinuation of the [clorazepate](#) therapy, the author feels that all patients receiving prescriptions for antidepressant and benzodiazepines should avoid the abrupt discontinuation of the benzodiazepine therapy.

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

### 3.3.9.K] Sleep disorder

1) [Imipramine](#) can markedly suppress REM sleep (REM time, REM activity, and number of REM periods) in adolescents and adults [173] Sleep disorders was among the most common event reported in enuretic children treated with [imipramine](#) hydrochloride. Insomnia may present as a manifestation of worsening depression [124].

### 3.3.9.L] Somnolence

1) Tricyclic antidepressants, including [imipramine](#), may cause drowsiness and fatigue [123][124].

### 3.3.9.M] Summary

1) The following neurologic adverse effects may occur with tricyclic antidepressants, including [imipramine](#): numbness, tingling, paresthesias of the extremities, ataxia, tremors, extrapyramidal symptoms, [peripheral neuropathy](#), weakness, drowsiness, dizziness, seizures, [cerebral ischemia \(stroke\)](#), EEG changes, confusional states with hallucinations especially in the elderly, disorientation, delusions, forgetfulness, anxiety, restlessness, agitation, insomnia, nightmares, [hypomania](#), and exacerbation of [psychosis](#) [123][124][112]. [Psychomotor impairment](#) [167], myoclonus [170], [akathisia](#) [171], [Tourette's syndrome](#) [172] and sleep disturbances [173] have been associated with the use of [imipramine](#).

### 3.3.9.N] Tremor

1) Imipramine-induced tremor occurred in a 61-year-old male. Following doses of 75 mg daily for 3 days, the patient developed a marked action tremor of the upper extremities which was smooth and rhythmic (6 to 9 cycles per second) and interfered with routine activities. The tremor did not worsen when the dose of [imipramine](#) was increased to 150 mg daily. [Propranolol](#) (20 mg twice a day) produced attenuation of the tremor within 25 to 48 hours [168].

2) Some patients with [panic disorder](#) [imipramine](#) therapy may develop a jitteriness syndrome [169]. This condition is characterized by jitteriness, restlessness, trouble sitting still, insomnia, increased energy, increased anxiety and a possible decreased serum iron level. Whether iron supplementation will prevent or treat this syndrome remains to be proven.

### 3.3.10] Ophthalmic Effects

#### 3.3.10.A] Abnormal vision

1) Tricyclic antidepressants, including [imipramine](#), may cause blurred vision, disturbances of accommodation and mydriasis [123][124].

### 3.3.11] Otic Effects

#### 3.3.11.A] Tinnitus

1) Tinnitus has been reported in 4 patients: a 37-year-old female, a 30-year-old female, a 15-year-old female, and a 31-year-old male, all receiving 50 to 150 mg [imipramine](#) daily. Tinnitus disappeared when the [imipramine](#) dose was reduced in the 3 females and the male required a change in therapy [209].

2) Five additional reports of tinnitus secondary to [imipramine](#) therapy have been published [210]. The patients had no history of tinnitus or other otologic abnormalities. All patients developed tinnitus during the second or third week of treatment, with doses of 150 to 250 mg daily of [imipramine](#) (combined plasma imipramine-desipramine levels between 200 to 450 nanograms/mL). The tinnitus subsided spontaneously within 2 to 4 weeks without any specific treatment in all patients (the dose of [imipramine](#) was maintained in 3 patients and increased in 2). Based upon a chart review of 475 patients treated at the University of Michigan Medical Center, the authors indicate that approximately 1% of patients receiving tricyclic antidepressants develop tinnitus.

3) A 38-year-old depressed female develop ringing in her ears one week after the dose of [imipramine](#) was increased to 100 mg/day [211]. She had no history of ear problems and denied using [aspirin](#) or other salicylates. The medication was continued since the tinnitus was only mildly bothersome and no abnormalities could be found on neuro- and physical examination. The dose of [imipramine](#) was increased to 150 mg/day during the second week. The tinnitus continued for approximately six weeks and then diminished without any changes in drug therapy.

### 3.3.12] Psychiatric Effects

#### 3.3.12.A] Aggressive behavior

1) A 26-year-old male treated with a single oral dose of [imipramine](#) for [cataplexy](#) developed a feeling of aggression which increased intensely over the next half hour with the patient struggling to keep control. The patient was noted to have shaky legs, staggering, and feelings of drunkenness. It was noted that the patient had previously received [diazepam](#) and [amitriptyline](#) [200]. In addition, increased aggression was reported in 2 depressed boys, ages 12 and 6 years, during [imipramine](#) therapy [201].

2) Four cases of rapid onset untoward aggressiveness was associated with the use of tricyclic antidepressants. In the first 2 cases the aggressive behavior coincided with the reintroduction of the tricyclic antidepressant. The mechanism of the paradoxical response of rapid onset and qualitative characteristics of their reaction are consistent with a probable site of action in the reticular formation which is the rational for their usefulness in [cataplexy](#) [202].

#### 3.3.12.B] Delirium



1) A 31-year-old hospitalized female developed [delirium](#) during [imipramine](#) therapy; the patient had no known risk factors [207]. Initially she presented with a hypomanic reaction (characterized by restlessness, hyperactivity, irritability, lability of mood, and insomnia) that later developed into the [delirium](#) reaction (disorientation to time and place, incoherent speech, periods of blank stares, periods of unresponsiveness, visual distortions, hallucinations) while on standard dose [imipramine](#) therapy. Plasma [imipramine](#) concentrations were in the low end of the therapeutic range. Thus, imipramine-induced [delirium](#) may occur in some patients as an idiosyncratic reaction unrelated to [imipramine](#) serum concentrations.

### 3.3.12.C] Depression, worsening

1) Clinical worsening of depression has been reported in patients receiving antidepressant therapy, particularly during the initial few months of treatment and during dose adjustments. It may persist until significant remission occurs. All patients treated with antidepressants for any indication should be monitored for signs of clinical worsening [123][124].

2) 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 worsening of their depression. This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms [123][124][199].

### 3.3.12.D] Mania

1) Manic or hypomanic episodes may occur with [imipramine](#) therapy, especially in patients with cyclic disorders. In such cases, discontinuation of the drug may be necessary [123].

### 3.3.12.E] Psychotic disorder

1) Exacerbation of [psychosis](#) may occur with tricyclic antidepressant treatment, including [imipramine](#) [123][124]. Psychotic reactions following doses of [imipramine](#) ranging from 75 to 600 mg/day have been reported. Symptoms have included disorientation, agitation, confusion, restlessness, insomnia, tremor, ataxia, hallucinations, paranoia and other abnormal manifestations. Some data suggests that these effects may occur more frequently in elderly patients and/or those receiving higher doses. Discontinuation of the drug results in improvement and disappearance of the symptoms [203][204][205][206].

### 3.3.12.F] Suicidal thoughts

#### 1) Adults

a) No clinically significant differences in the risk of suicide and suicide attempts were observed across antidepressant agents and antidepressant classes in a 9-year, population-based cohort study consisting 287,543 adults. Based on the health care utilization data, the overall combined event rates of suicide death or hospitalization due to self harm ranged from 4.41 to 9.09 per 1000 person years. Among patients who received tricyclic antidepressants, including, [imipramine](#) 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 [198].

**b))** 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 [123][124].

## 2) Pediatrics

**a))** 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 [123][124].

**b))** 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 [199].

## 3) Management

**a))** 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. Closely monitor patients especially during the initial few months of therapy or at times of dose changes [123][124][199].

### 3.3.12.G] Suicide

1) Suicide has been reported in adult patients receiving antidepressant therapy in clinical trials; however, the number of suicides was insufficient to determine causality [123][124].

2) 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, [imipramine](#) 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 [198].

### 3.3.12.H] Summary

1) Paranoia, aggressive behavior, [200][201] agitation, delusions [112], and [delirium](#) [207] have occurred with [imipramine](#) therapy. [Suicidal ideation](#), worsening of depression, mania, and [hypomania](#) are also potential side effects of [imipramine](#) [123][124][208].

## 3.3.13] Renal Effects

### 3.3.13.A] Delay when starting to pass urine

1) Tricyclic antidepressants, including [imipramine](#), may cause delayed micturition [123][124].

### 3.3.13.B] Nephrotoxicity

1) A 65-year-old white male was treated with doses of up to 100 mg three times/day of [imipramine](#) for 24 days for depression developed renal damage [185]. The patient developed symptoms of anorexia, nausea, confusion, disorientation, and tremulousness in association with elevated BUN (80 mg/dL) and [creatinine](#) (2.5 mg/dL) values. Urine output fell to 725 mL/day despite a fluid intake of approximately 2.5 L. Discontinuation of [imipramine](#) resulted in improvement of this clinical condition and abnormal laboratory values returning to normal by the third day.

### 3.3.13.C] Urinary retention

1) Tricyclic antidepressants, including [imipramine](#), may cause urinary retention [123][124].

## 3.3.14] Reproductive Effects

### 3.3.14.A] Sexual dysfunction

1) [Erectile dysfunction](#) and ejaculatory delay or loss has been reported in depressed and normal patients, at a minimum daily dose of 75 mg. Pain on ejaculation [212][213][214][215] and loss of libido [216] as well as increased libido has been reported [213].

2) The occurrence of sexual dysfunction associated with antidepressant therapy is frequent. Decreases in sexual function occurs in 8% of males and 16% of females treated with placebo, 80% of males and 57% of females treated with [phenelzine](#), and 50% of males and 27% of females treated with [imipramine](#) [217].

Sexual dysfunctions reported include decrease in libido, excitement, and orgasm and a delay in ejaculation. Similar results have been reported more recently by the same group of investigators [218].

3J) Other investigators feel that long-term treatment with [imipramine](#) has no negative effect on sexual function [219]. Instead they feel that the presence of depressive symptoms is associated with diminished libido or decreased sexual pleasure. An evaluation of 90 patients with a [major depressive disorder](#) treated with [imipramine](#) found no relationship between [imipramine](#) and sexual function in the total group or the females alone. The number of males included in the study was inadequate to draw any conclusions regarding population.

4J) A 51-year-old male was treated with an initial dose of 75 mg/day which was reduced to oral [imipramine](#) 25 mg/day for 2 to 3 weeks and developed erectile impotence at the higher dose. Potency rapidly returned upon decreasing the drug dosage to 25 mg/day [214].

5J) [Anorgasmia](#) has been reported in a woman treated with [imipramine](#) therapy and disappeared when [desipramine](#) therapy was substituted for the [imipramine](#) [220].

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION

#### 3.3.14.BJ Swelling of testicle

1J) Tricyclic antidepressants, including [imipramine](#), may cause testicular swelling [123][124].

### 3.3.15 Respiratory Effects

#### 3.3.15.AJ Acute respiratory distress syndrome

1J) A 15-year-old was admitted to the emergency department following the ingestion of 5 grams (150 mg/kg) of [imipramine](#) approximately 45 minutes prior to arrival [191]. Within 5 hours of ingestion the patient developed severe hypoxemia, increased QS/QT, and [decreased lung compliance](#). At that time a diagnosis of adult [respiratory distress syndrome](#) (ARDS) was made. [Positive end-expiratory pressure](#) (PEEP) resulted in an improvement in [lung compliance](#), hypoxemia, and shunting. Whether or not the development of adult [respiratory distress syndrome](#) was a direct result of the [imipramine overdose](#) or the development of bradycardia, hypoxemia, [metabolic acidosis](#), hypotension or [physostigmine](#) therapy remains unknown.

### 3.3.16 Other

#### 3.3.16.AJ Drug fever

1J) Tricyclic antidepressants, including [imipramine](#), may cause drug fever [123][124].

#### 3.3.16.BJ Fatigue

1J) Tricyclic antidepressants, including [imipramine](#), may cause fatigue [123][124].

#### 3.3.16.CJ Tachyphylaxis

1J) Tolerance to the therapeutic effects of [imipramine](#) therapy has been reported in a small number of patients [221]. Usually these patients initially respond to therapy and then weeks to months later they [relapse](#) despite continued antidepressant therapy. Remission can usually be regained by increasing the dose of the medication or changing the medication. The exact mechanism for the development of this tolerance is not known.

#### 3.3.16.DJ Withdrawal sign or symptom

1J) Withdrawal symptoms have been associated with the discontinuation of tricyclic antidepressant therapy and may occur in 21 to 55% of the patients. These symptoms frequently occur within the first 24 to

48 hours after cessation of therapy. The withdrawal period is characterized by general somatic malaise (muscle aches, coryza, excessive sweating), gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), motor restlessness, and/or neuropsychiatric symptoms (drowsiness, apathy, irritability, agitation, and recurrence of depressed mood). Restarting [imipramine](#) therapy generally improves the condition. To prevent the occurrence of this withdrawal reaction, the [imipramine](#) therapy should be withdrawn gradually, when possible [222][223][224][225][226].

2)) Children withdrawn from high-dose [imipramine](#) therapy over 3 to 10 days may develop a withdrawal syndrome [227]. The syndrome is characterized by nausea, vomiting, decreased appetite, tearfulness, headaches, agitation, and malaise. It is thought that this withdrawal syndrome may be the result of a cholinergic rebound following the discontinuation of highly anticholinergic medications. Extending the duration of the tapering period may be helpful in avoiding the occurrence of this syndrome, but there is no clinical evidence to support this theory.

3)) A 53-year-old woman, with a 25-year history of [unipolar depression](#) but no evidence of bipolar illness, developed a fast-cycling [bipolar disorder](#) following abrupt discontinuation of her long-term tricyclic antidepressant therapy [228]. The bipolar illness presented as [hypomania](#) 2 days after stopping drug therapy. The hypomanic period was followed by severe depression and subsequent fluctuation between mania and depression, each lasting from 2 to 8 weeks.

4)) Multifocal [premature ventricular contractions](#) (PVCs) occurred in a 62-year-old woman following withdrawal of [imipramine](#). The depressed woman had preexisting [nonspecific intraventricular conduction delay](#) [137]. [Imipramine](#) (300 mg daily) was tapered over a 4-day period, and then [doxepin](#) was initiated at a dose of 50 mg at bedtime. PVCs and [couplets](#) were observed the day following discontinuance of [imipramine](#). Reinitiation of [imipramine](#) therapy (100 mg daily) produced normal sinus rhythm with only occasional uniform PVCs, and no [couplets](#), multiforms, runs, or pauses. It was felt that withdrawal of the drug resulted in rebound irritability with resultant aberrant rhythms. Tricyclic antidepressants should be withdrawn gradually, with frequent EKG monitoring, in patients with a preexisting conduction defects. In patients with no suspected conduction defect, monitoring for signs of ectopy should be undertaken during withdrawal.

5)) Withdrawal of [imipramine](#) therapy used to treat postpsychotic depression after six months in six schizophrenic patients resulted in depressive [relapses](#) [229]. All six patients had benefit from the initial addition of [imipramine](#) to their [fluphenazine](#) decanoate and [benztropine](#) therapy. After six months the dose of [imipramine](#) was decreased by 50 mg/day at weekly intervals without the patient knowledge until it was discontinued. All six patients had experienced recurrence of a depressive-like state and three manifested a coincident exacerbation of psychotic symptoms. While only one of four patient maintained on all three drugs experienced a depressive-like [relapse](#).

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

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

##### 1)) 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

##### 2)) Crosses Placenta: Yes

##### 3)) Clinical Management

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

#### 4)) Literature Reports

a)) [Imipramine](#) has been associated with [teratogenic effects](#), however, a clear causal relationship has not been established. In the large cohort study [987], of 19 mother-child pairs exposed to [imipramine](#) in the first trimester, 2 malformations were reported, suggesting an increased risk of [teratogenic effects](#).

b)) A review of the Finnish register of [congenital malformations](#) for 1964 to 1972 revealed 3 possible cases of [teratogenic effects](#) (2 [cleft lips](#), 1 CNS anomaly) that were related to the use of an [imipramine](#)/chloropyramine combination [988].

c)) Neonatal intoxication and withdrawal symptoms may be observed with maternal use of [imipramine](#). Symptoms observed in the neonate include cyanosis, respiratory distress, vasomotor instability, irritability, hypokinesia, convulsions, jerky movements, increased respiratory rate, autonomic dysfunction, hypoactivity, and belly dance movements of the abdomen before voiding [989][990].

d)) Several infants have been described who developed transient respiratory and neurological symptoms shortly after birth, possibly in relation to maternal [imipramine](#). Of 3 infants whose mothers had used [imipramine](#) throughout the pregnancy, the infants developed postnatal symptoms of irritability, restlessness, inconsolable crying, tachypnea, cyanosis, hypotonia, muscle fasciculations, and tremors. One infant developed signs of [heart failure](#) despite a normal [electrocardiogram](#), a heart rate of 160 to 180 per minute, and absence of a congenital cardiac malformation. One infant experienced [laryngeal spasms](#) and feeding difficulties [991].

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 [imipramine](#) throughout gestation when compared to controls [992]. 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 [992].

#### B)) Breastfeeding

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

2)) Thomson Lactation Rating: Infant risk cannot be ruled out.

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

#### 3)) Clinical Management



a)) Imipramine and its metabolite, desipramine, appear in breast milk in low concentrations. The potential for adverse effects in the nursing infant has not been evaluated. When the maternal dose is high, exposure of the infant to the drug may be minimized by limiting the number of feeds per day [995].

#### 4)) Literature Reports

a)) The amount of imipramine and desipramine available to an infant is small. The amount of imipramine measured in breast milk was 4 to 29 ng/mL and desipramine was 17 to 35 ng/mL; a milk:plasma ratio of 1 has been suggested [994].

#### 5)) Drug Levels in Breastmilk

##### a)) Parent Drug

##### 1)) Milk to Maternal Plasma Ratio

a)) 1 [1036]

##### b)) Active Metabolites

1)) desipramine [1035]

### 3.5] Drug Interactions

#### 3.5.1] Drug-Drug Combinations

##### 3.5.1.A] Acecainide

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

2)) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide[424], amiodarone [425], azimilide [426], bretylium [427], ibutilide [428], sotalol [431]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [432][433].

3)) Severity: major

4)) Onset: rapid

5)) Substantiation: theoretical

6)) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7)) Probable Mechanism: additive QT prolongation

8)) Literature Reports

a)) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves [422].

b)) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised [423].

### 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[531][532]. Considerable interindividual differences may be found [533].
- 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 [528]. 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 [529]. 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 [530]. 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] Alfuzosin

- 1)) Interaction Effect: an increased risk of QT interval prolongation
- 2)) Summary: Use caution when using [alfuzosin](#) and [imipramine](#) concomitantly due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#)[878]. If concurrent administration is required, monitor closely for QT interval prolongation.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution when using [alfuzosin](#) and [imipramine](#) concomitantly due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects[878]. If concurrent administration is required, monitor closely for QT interval prolongation.
- 7)) Probable Mechanism: additive effects on QT interval prolongation



## 8) Literature Reports

a) In a postmarketing study that evaluated the effect of concomitant administration of [alfuzosin](#) with another QT interval-prolonging drug of similar effect size, the observed QT interval prolongation was greater than that seen with either drug alone, but was not more than additive. The corrected (Fridericia) QT interval (QTcF) increased by 5.9 milliseconds (upper bound of 95% confidence interval (CI), 9.4 milliseconds). The QTcF increase observed with [moxifloxacin](#) 400 mg (positive control) was 10.2 milliseconds (upper bound 95% CI, 13.8 milliseconds). The mean placebo-subtracted QTcF increase following administration of [alfuzosin](#) 10 mg alone was 1.9 milliseconds (upper bound 95% CI, 5.5 milliseconds) [878].

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

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

2) Summary: Both [almotriptan](#), a serotonin receptor agonist, and [imipramine](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#)[388]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [almotriptan](#) and [imipramine](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [378].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [almotriptan](#) and [imipramine](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[388]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

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

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

2) Summary: [Imipramine](#) steady state plasma concentrations increased an average of 31% when used concomitantly with [alprazolam](#) at doses up to 4 mg/day. The clinical significance of this increase is unknown. A decrease in the [imipramine](#) dose should be considered for patients who are being treated with [alprazolam](#) and [imipramine](#) concurrently and who experience an increase in side effects such as dry eyes and mouth, constipation, decreased urination, or [arrhythmias](#)[957].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of [alprazolam](#) and [imipramine](#) may increase the plasma concentrations of [imipramine](#). The clinical significance of this increase is unknown. If signs or symptoms of increased [imipramine](#) exposure such as blurred vision, dry mouth, constipation, urinary retention, or [arrhythmias](#) are noticed, a downward dosage adjustments of [imipramine](#) should be considered.

7) Probable Mechanism: unknown

**3.5.1.F] Amiodarone**

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

2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[424], [amiodarone](#) [425], azimilide [426], [bretylium](#) [427], [ibutilide](#) [428], sematilide [429], [dofetilide](#) [430], and [sotalol](#) [431]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [432][433].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [422].

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetry monitoring is advised [423].

**3.5.1.G] Amisulpride**

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

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride[334], [haloperidol](#) [335], [risperidone](#) [336], sertindole [337], [quetiapine](#) [338], sultopride [339], and zotepine [340]. Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended [341][342].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [333].

**3.5.1.H] Amitriptyline**

- 1J) Interaction Effect: an increased risk of QT interval prolongation; an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2J) Summary: Concomitant use of [amitriptyline](#) and [imipramine](#) is not common clinical practice. However if using [amitriptyline](#) and [imipramine](#) concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[377]. Both [amitriptyline](#), a serotonin reuptake inhibitor [377], and [imipramine](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [imipramine](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, and diarrhea), and mental status changes (eg, agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [378].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of [amitriptyline](#) and [imipramine](#) is not common clinical practice. However if using [amitriptyline](#) and [imipramine](#) concomitantly, use caution due to a potential for additive effects on the QT interval and an increased risk of serious cardiovascular effects and/or additive serotonergic effects and an increased risk of [serotonin syndrome](#)[377].
- 7J) Probable Mechanism: additive effects on the QT interval; additive serotonergic effect

### 3.5.1.1J [Amobarbital](#)

- 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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. These drugs also have additive CNS and respiratory depressant effects.
- 3J) Severity: minor
- 4J) Onset: delayed
- 5J) Substantiation: probable
- 6J) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
- 7J) Probable Mechanism: increased tricyclic antidepressant metabolism
- 8J) Literature Reports

aJ) The pharmacokinetics of a single oral dose of [desipramine](#) (100 mg) were studied in eight epileptic patients chronically treated with [phenobarbital](#) and in eight drug-free healthy controls [560]. 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: Concomitant use of [amoxapine](#) and [imipramine](#) is not common clinical practice. However, if both drugs are used concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[241].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [amoxapine](#) and [imipramine](#) is not common clinical practice. However, if both drugs are used concomitantly, use caution due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[241].
- 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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 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](#)[592].

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] [Anisindione](#)

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[717][718]. Considerable interindividual differences may be found [719].

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 [714]. 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 [715]. 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 [716]. 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.N] [Apomorphine](#)

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

2)) Summary: Concomitant use of [apomorphine](#) and [imipramine](#) may result in [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)). Therefore, caution should be used when these agents are given concurrently[707]. If concomitant therapy is required, closely monitor for QT interval prolongation.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [apomorphine](#) and [imipramine](#) may result and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)). Therefore, caution should be used when these agents are given concurrently[707]. If concomitant therapy is required, closely monitor for QT interval prolongation.

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

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

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

2))Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended[773][774][775].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepressant is not recommended.

7)) Probable Mechanism: additive effects on QT prolongation

8)) Literature Reports

a)) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [771].

b)) A 68-year-old man suffering from agitated [major depression](#) was begun on a dose of [desipramine](#) 125 mg daily which produced a subtherapeutic serum level of 442 nmol/L (therapeutic



range = 500 to 1000 nmol/L). An increased dose of 175 mg daily produced excellent clinical response with no side effects. He developed [atrial fibrillation and flutter](#). [Digoxin](#) 0.25 mg daily was added to his therapy, and [desipramine](#) was discontinued. His [arrhythmia](#) was suppressed with the addition of [propafenone](#) 150 mg twice daily and 300 mg at bedtime. [Desipramine](#) 150 mg daily was again begun, at which point he experienced dry mouth, sedation, and shakiness; the [desipramine](#) serum level was measured at 2092 nmol/L. The [desipramine](#) was discontinued for five days, the side effects ceased, and [desipramine](#) therapy was resumed at 75 mg daily. The [desipramine](#) serum level was measured at 1130 nmol/L [772].

### 3.5.1.P] Aprobarrital

- 1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
- 2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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[654].
- 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[650]. 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[650].
- 7) Probable Mechanism: potentiation of cardiovascular effects

**3.5.1.S] Arsenic Trioxide**

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with [arsenic trioxide](#). Possible pharmacodynamic interactions can occur between [arsenic trioxide](#) and potentially arrhythmogenic agents such as tricyclic antidepressants that prolong the QT interval[820]. Even though no formal drug interaction studies have been done, the coadministration of [arsenic trioxide](#) and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [821][822].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [arsenic trioxide](#) and other drugs that may prolong the QTc interval, such as tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports

a) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving [amitriptyline](#), compared to zero out of 53 in the control group using a hospital based information system. The authors recommended that [amitriptyline](#) not be used in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful [817][818].

b) QT/QTc prolongation should be expected during treatment with [arsenic trioxide](#) and [torsade de pointes](#) as well as [complete heart block](#) has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with [arsenic trioxide](#) were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after [arsenic trioxide](#) infusion, and then returned towards baseline by the end of 8 weeks after [arsenic trioxide](#) infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age [819].

**3.5.1.T] Asenapine**



- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: The concomitant use of asenapine with other drugs that may cause QT interval prolongation, such as [imipramine](#), should be avoided due to an increased risk of QT interval prolongation and serious cardiac adverse events. Additionally asenapine is a weak CYP2D6 inhibitor and[404] [imipramine](#) is a CYP2D6 substrate [241].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of asenapine with other drugs that may cause QT interval prolongation, such as [imipramine](#), should be avoided due to an increased risk of QT interval prolongation and serious cardiac adverse events[404].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.U] [Astemizole](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of [astemizole](#) and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended[824][825].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [astemizole](#) and agents that prolong the QT interval, such as tricyclic antidepressants, is not recommended.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports

a) A comprehensive discussion of the cardiovascular effects of tricyclic antidepressants has been presented [823]. [Electrocardiogram](#) effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves.

### 3.5.1.V] [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[542].
- 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.W] [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 [imipramine](#). The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with [imipramine](#), 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[831].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Dosage adjustment of [atomoxetine](#) may be necessary when coadministered with [imipramine](#).
- 7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of [atomoxetine](#) by [imipramine](#)

### 3.5.1.X] Azimilide

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[424], [amiodarone](#) [425], [azimilide](#) [426], [bretylum](#) [427], [ibutilide](#) [428], [semitilide](#) [429], [dofetilide](#) [430], and [sotalol](#) [431]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [432][433].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [422].

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised [423].

### 3.5.1.Y] Azithromycin

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Use caution when using [azithromycin](#) and [imipramine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[402][241].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Use caution when using [azithromycin](#) and [imipramine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[402] [241].

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.Z] 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[380]. 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.AA] 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[380]. 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.AB] Bepridil

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

- 2) Summary: In US clinical trials, the QT and QTc intervals were commonly prolonged by [bepridil](#) in a dose-related fashion[289]. Tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose [290].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [bepridil](#) and other drugs which may prolong the QTc interval, including tricyclic antidepressants, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.AC] 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[535][536][537].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The combination of bethanidine and [imipramine](#), 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 [534].

### 3.5.1.AD] Bretylium

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[424], [amiodarone](#) [425], azimilide [426], [bretylium](#) [427], [ibutilide](#) [428], sotalol [429], [dofetilide](#) [430], and [sotalol](#) [431]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [432][433].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [422].

b)) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised [423].

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

- 1)) Interaction Effect: increased [imipramine](#) plasma level
- 2)) Summary: [Bupropion](#) was reported to decrease clearance and increase plasma levels of [imipramine](#) and its primary metabolite [desipramine](#) in a 64-year-old woman[399]. Coadministration of [bupropion](#) with drugs that are metabolized by the cytochrome P450 2D6 isoenzyme, such as [imipramine](#), should be approached with caution and should be initiated at the lower end of the dose range of [imipramine](#). If [bupropion](#) is added to the treatment regimen of a patient already receiving [imipramine](#), a decrease in the dose of [imipramine](#) should be considered [400][401].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: theoretical
- 6)) Clinical Management: When [imipramine](#) is given with [bupropion](#), monitor for signs of [imipramine](#) toxicity or monitor [imipramine](#) plasma concentrations. Coadministration of [imipramine](#) with [bupropion](#) should be approached with caution and should be initiated at the lower end of the dose range of [imipramine](#). If [bupropion](#) is added to the treatment regimen of a patient already receiving [imipramine](#), consider decreasing the dose of [imipramine](#).
- 7)) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated [imipramine](#) metabolism
- 8)) Literature Reports

a)) [Bupropion](#) was reported to decrease clearance and increase plasma levels of [imipramine](#) and its primary metabolite [desipramine](#) in a 64-year-old woman. This patient was treated with [imipramine](#) for 8 years prior to addition of [bupropion](#) to therapy. Estimated [imipramine](#) clearance decreased from 1.7 mL/min without [bupropion](#) to 0.73 mL/min with [bupropion](#). Additional studies are needed to confirm this observation [398].

### 3.5.1.AF] [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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.AG] [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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.AH] [Butalbital](#)

1) Interaction Effect: decreased efficacy of [imipramine](#)

2) Summary: A 44-year old female on [imipramine](#) therapy experienced a [relapse](#) of her [depressive disorder](#) following the use of a butalbital-containing product for headaches. Her [imipramine](#) concentration decreased by approximately 50%, which was attributed to an induction of cytochrome P450 1A2 enzymes caused by [butalbital](#)[728].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable



- 6) Clinical Management: [Imipramine](#) serum levels should be measured one week after the addition of [butalbital](#) therapy, and dosage adjustments should be based on the results of the [imipramine](#) level and on the patient's response.
- 7) Probable Mechanism: induction of [imipramine](#) metabolism by [butalbital](#)
- 8) Literature Reports

a) A 44-year old woman was admitted to a psychiatric unit for an exacerbation of her depression. At the time, her antidepressant regimen included [imipramine](#) 300 mg daily, with an [imipramine](#) concentration of 174 ng/mL and [desipramine](#) concentration of 134 ng/mL. These levels were considered within the normal range, and were consistent with her past concentrations. Because of recurring headaches, she was prescribed a product containing [butalbital](#) 50 mg, and required 8 tablets ([butalbital](#) 400 mg) daily to control her headaches. The patient progressed well until two weeks into her hospital stay, when she again experienced a [relapse](#) of her [depressive disorder](#). Concentrations at this time were [imipramine](#) 48 ng/mL and [desipramine](#) 122 ng/mL. [Butalbital](#) was the most reasonable explanation for the decreased [imipramine](#) levels, so it was discontinued and [imipramine](#) was increased to 325 mg daily. However, further attempts at documenting a return to normal [imipramine](#) concentrations were futile, since the patient restarted the butalbital-containing product from her stockpile at home [727].

### 3.5.1.AII 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[540][541].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Caution is advised if patients use cannabis with a tricyclic antidepressant. Monitor heart rate changes closely.
- 7) Probable Mechanism: possibly due to beta-adrenergic effect of cannabis coupled with the anticholinergic effect of tricyclic antidepressants
- 8) Literature Reports

a) A 21-year-old female receiving oral [nortriptyline](#) 30 milligrams at bedtime for 9 months developed marked [sinus tachycardia](#) (160 beats/minute) within 30 minutes of smoking a cannabis cigarette. The patient's heart rate was about 90 beats/minute before smoking the cannabis. She had used cannabis many times before starting the [nortriptyline](#) without ill effects [538].

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



Case 4, a 16-year-old male taking [desipramine](#) and [clonidine](#) reported hallucinations, confusion, mild shortness of breath, and elevated heart rate after smoking marijuana. This was different than the effect he experienced prior to taking [desipramine](#) [539].

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

- 1J) Interaction Effect: decreased [imipramine](#) effectiveness
- 2J) Summary: In a retrospective study of 36 children suffering from hyperactivity secondary to [attention deficit disorder](#), the antidepressant levels ([imipramine](#) and its metabolite [desipramine](#)) were decreased by 50% in children receiving [carbamazepine](#) compared to levels obtained with [imipramine](#) alone[293].
- 3J) Severity: moderate
- 4J) Onset: delayed
- 5J) Substantiation: probable
- 6J) Clinical Management: Monitor for clinical efficacy of the [imipramine](#) 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 [imipramine](#) metabolism
- 8J) Literature Reports

aJ) In a retrospective study, of 36 children with [attention deficit hyperactivity disorder](#), the average plasma concentration of [imipramine](#) was significantly lower in patients treated with [carbamazepine](#) concurrently. The average dose of [imipramine](#) was 1.3 mg/kg in patients receiving [imipramine](#) alone, compared to an [imipramine](#) dose of 1.8 mg/kg in patients receiving both [imipramine](#) and [carbamazepine](#). The plasma level of [imipramine](#), [desipramine](#), and total tricyclic antidepressant plasma levels were significantly lower in patients treated with [carbamazepine](#) concurrently. The dose of [imipramine](#) may need to be increased if [carbamazepine](#) is added to therapy and the dose of [imipramine](#) may need to be decreased if [carbamazepine](#) is stopped [291].

bJ) Combination therapy with [carbamazepine](#) decreases steady-state total serum concentrations of [imipramine](#) and mean concentrations of [desipramine](#). Thirteen patients were treated with [imipramine](#) 2 mg/kg/day for 3 weeks, after which [carbamazepine](#) 400 mg/day was added. The ratios of total concentrations of [imipramine](#) to [desipramine](#) were similar before and two weeks after [carbamazepine](#) intake (0.7 +/- 0.41 versus 0.63 +/- 0.36; p greater than 0.05). Free fractions of [imipramine](#) and [desipramine](#) were elevated after the addition of [carbamazepine](#). Despite lower [imipramine](#) and [desipramine](#) total concentrations, the combination treatment with [carbamazepine](#) in depressed patients is effective and well tolerated. Dosage increase of [imipramine](#) does not appear to be necessary in the depressed patients included in this study [292].

### 3.5.1.AK] [Chloral Hydrate](#)

- 1J) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2J) Summary: [Chloral](#) hydrate and tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose[418][419]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: The concurrent administration of [chloral](#) hydrate and a tricyclic antidepressant is not recommended.
- 7J) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.AL] Chloroquine

- 1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsades de pointes**, cardiac arrest)
- 2) Summary: **Chloroquine** can prolong the QT interval in some patients, which may result in **ventricular tachycardia**, **ventricular fibrillation**, and **torsades de pointes**. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of **arrhythmias**, the concurrent administration of **chloroquine** and tricyclic antidepressants is not recommended[392][393].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of **chloroquine** and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.AM] 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[664], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [665]. The effects of the interaction appear to be estrogen dose-related [666] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on **estrogen therapy** [667].
- 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: unknown
- 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, ten 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 ten patients that received placebo did not improve over the six weeks of the study. The ten patients taking estrogen and **imipramine** demonstrated a significantly greater improvement in symptoms than did the ten patients taking **imipramine** alone. However, after two weeks, the five 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 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 ten patients receiving only **imipramine**. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [655].

b)) A case reported demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 mg and [imipramine](#) 100 mg [656]. The patient developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [657].

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 [658].

d)) The effects of oral contraceptives on [clomipramine](#) were studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 mg at bedtime while 19 took [clomipramine](#) 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [659].

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 [660].

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 [661].

g)) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [662]. 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 [663].

### 3.5.1.AN] [Chlorpromazine](#)

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

- 2j) Summary: Use caution when using [chlorpromazine](#) and [imipramine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[683]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.
- 3j) Severity: major
- 4j) Onset: unspecified
- 5j) Substantiation: theoretical
- 6j) Clinical Management: Use caution when using [chlorpromazine](#) and [imipramine](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[683]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.
- 7j) Probable Mechanism: additive effects on the QT interval

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

- 1j) Interaction Effect: [imipramine](#) toxicity (dry mouth, urinary retention, blurred vision)
- 2j) Summary: Concomitant [cimetidine](#) and [imipramine](#) therapy has resulted in inhibition of the metabolism of [imipramine](#), leading to prolonged half-life and elevated serum concentrations[738][739][740] and adverse effects [738][741][739].
- 3j) Severity: moderate
- 4j) Onset: delayed
- 5j) Substantiation: probable
- 6j) Clinical Management: [Imipramine](#) levels should be considered within the first few days of starting or discontinuing [cimetidine](#). An alternative H2 blocker that does not appear to impair the metabolism of [imipramine](#), such as [ranitidine](#) or [famotidine](#), might be considered.
- 7j) Probable Mechanism: decreased [imipramine](#) metabolism
- 8j) Literature Reports

a) In a case report, a 32-year-old woman concurrently on [cimetidine](#) 300 mg four times daily for abdominal distress exhibited severe anticholinergic side effects and orthostatic hypotension with the addition of [imipramine](#), 75 to 125 mg daily [732]. Upon rechallenge, [imipramine](#) pharmacokinetics with and without [cimetidine](#) were evaluated. With concurrent administration of [cimetidine](#) 300 mg four times daily and [imipramine](#) 100 mg daily, steady state elimination half-life for [imipramine](#) was 44 hours and plasma clearance 210 mL/minute. The ratio of [imipramine](#) to [desipramine](#) was calculated to be 2.6 (normal ratio 1 to 1.2). Upon discontinuation of [cimetidine](#) the elimination half-life of [imipramine](#) decreased to 23 hours and the plasma clearance increased to 355 mL/minute. The patient was able to continue [imipramine](#) without complaints of anticholinergic side effects without [cimetidine](#). [Cimetidine](#) also was reported to increase the absolute bioavailability of oral [imipramine](#) doses in six healthy volunteers, in addition to impairing [imipramine](#) clearance and increasing the [desipramine](#) area under the curve [733].

b) Six healthy young (24 to 25 year-old) volunteers participated in four randomly sequenced clinical trials to assess the effects of [cimetidine](#) administration on the pharmacokinetics of [imipramine](#). Each clinical trial was separated by at least 1 week. Trial 1: 12.5 mg of [imipramine](#) was infused over 30 minutes. Trial 2: 300 mg of [cimetidine](#) was administered orally every six hours, starting 12 hours prior to the [imipramine](#) dose (12.5 mg intravenously infused over 30 minutes) and continued for 96 hours after the [imipramine](#) dose. Trial 3: 50 mg of [imipramine](#) was administered orally following an overnight fast, with the fast continued for three hours following administration of the drug. Trial 4: [Cimetidine](#) was administered as described in trial 2 and 50 mg [imipramine](#) was administered oral as described in trial 3. The elimination half-life for [imipramine](#) was significantly increased (15.5 hours to 22.1 hours) during [cimetidine](#) therapy in the intravenous administration group and increased (15.3 hours to 20.7 hours), but not significantly, in the oral

administration group. Absolute bioavailability for orally administered [imipramine](#) nearly doubled (40% to 75%) during [cimetidine](#) treatment. Based on these results patients receiving concurrent [cimetidine](#) and [imipramine](#) therapy should have a 50% to 60% reduction in [imipramine](#) dose in order to avoid potential [imipramine](#) toxicity or should have their plasma [imipramine/desipramine](#) levels monitored closely [734].

c) Concomitant administration of [cimetidine](#) and [imipramine](#) was reported to result in [psychosis](#) (in the presence of a clear sensorium) in a 38-year-old woman with [major depression](#). Discontinuation of both drugs resulted in resolution of [psychosis](#) and depression within 72 hours. However, it is unclear if this patient's psychotic features were induced solely by the combination of these two agents [735].

d) The impaired elimination of these tricyclic antidepressants is rather rapid and new steady state serum concentrations would be expected to be achieved in three to five days after initiation of [cimetidine](#) therapy. It is suggested that [imipramine](#) doses be adjusted downward by 50% when [cimetidine](#) is given concurrently with further adjustments in doses being determined by plasma level monitoring [736].

e) Using microsomes from 4 human livers, [cimetidine](#) was shown to inhibit the demethylation of [imipramine](#) and the hydroxylation of desmethylinipramine [737].

### 3.5.1.AP| [Cinacalcet](#)

1) Interaction Effect: increased [imipramine](#) 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 [imipramine](#) are coadministered, dose adjustments of [imipramine](#) may be required[408]. Monitoring of [imipramine](#) plasma concentrations is recommended during the concomitant use of [imipramine](#) with a CYP2D6 inhibitor, such as [cinacalcet](#). Dose adjustments of one or both drugs, especially during therapy initiation and discontinuation, may be warranted [241].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: If [cinacalcet](#) is coadministered with a tricyclic antidepressant (TCA), such as [imipramine](#), a dose reduction of the TCA may be necessary[408]. Monitoring of [imipramine](#) plasma concentrations is recommended during the concomitant use of [cinacalcet](#) with [imipramine](#). Dose adjustments of one or both drugs, especially during therapy initiation and discontinuation, may be warranted [241].

7) Probable Mechanism: inhibition of CYP2D6-mediated [imipramine](#) metabolism by [cinacalcet](#)

### 3.5.1.AQ| [Ciprofloxacin](#)

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

2) Summary: Concomitant use of [ciprofloxacin](#) and [imipramine](#) 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[279]. 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 [imipramine](#) may increase the potential for serious [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)) and should be undertaken with caution. Geriatric patients may be particularly sensitive to QT prolongation[279]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.

7) Probable Mechanism: additive effects on the QT interval

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

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

2) Summary: [Cisapride](#) therapy has resulted in serious [cardiac arrhythmias](#), including [ventricular tachycardia](#), [ventricular fibrillation](#), [torsades de pointes](#), and QT prolongation. Because tricyclic antidepressant agents also may prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [cisapride](#) with a drug from this class is contraindicated[372].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of [cisapride](#) and tricyclic antidepressants is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

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

1) Interaction Effect: an increase in the bioavailability and half-life of [desipramine](#), the major metabolite of [imipramine](#)

2) Summary: [Imipramine](#) pharmacokinetics were not influenced by [citalopram](#) when the two were coadministered[961][962]. However, [citalopram](#) may increase exposure to [desipramine](#), the major metabolite of [imipramine](#). Clinical events have not been reported and, in an isolated report, [citalopram](#) was successfully substituted for [paroxetine](#) in a patient who had experienced elevated tricyclic antidepressant levels during [paroxetine](#) treatment. Citalopram is an inhibitor of cytochrome P450 2D6 enzymes, and [imipramine](#), a tertiary amine, is converted to a secondary amine ([desipramine](#)) by N-demethylation. The secondary amine then undergoes hydroxylation, a process which is controlled by the oxidative enzymes of the CYP2D6 system [963].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Caution is indicated in the coadministration of tricyclic antidepressants and [citalopram](#). Consider monitoring tricyclic antidepressant concentration and/or dose adjustment when there is a change in therapy or dose of [citalopram](#). However, [citalopram](#) may be preferred over [paroxetine](#) when tricyclic antidepressants are coadministered.

7) Probable Mechanism: inhibition of [desipramine](#) metabolism, the major metabolite of [imipramine](#)

8) Literature Reports

a) Eight healthy male volunteers completed three phases of an interaction study to determine the effects of coadministered [imipramine](#) and [citalopram](#). All subjects were extensive metabolizers of sparteine, indicating normal cytochrome P450 2D6 enzyme activity. Each subject received [citalopram](#) 40 mg alone as a single daily dose for 10 days, [imipramine](#) 100 mg as a single oral dose, and a single oral dose of [imipramine](#) 100 mg coadministered on day 7 of [citalopram](#) therapy. At least two weeks separated each treatment phase. Results showed that the concurrent administration of [citalopram](#) and [imipramine](#) resulted in a 50% increase in the [desipramine](#) area under the concentration-time curve (AUC) and a similar decrease in the 2-hydroxy-desipramine AUC. Also, the [desipramine](#) half-life was approximately seven hours longer when administered with [citalopram](#) (27 hours vs. 20 hours). The AUC and half-life of [imipramine](#) were not affected



by [citalopram](#) administration. These results showed that [citalopram](#) is an inhibitor of cytochrome P450 2D6 hepatic enzymes, since most tricyclic antidepressants rely on this system for metabolism [959].

b)) A case report describes a 45-year-old white female with [major depressive disorder](#) and [dysthymia](#). This patient failed several trials of antidepressants from all available drug classes, as well as [electroconvulsive therapy](#). The patient's medications included [pindolol](#), [desipramine](#), [clonazepam](#), and [olanzapine](#). [Paroxetine](#) was initiated and titration to 40 mg/day occurred over 3 months. The patient developed light-headedness, ataxia, and increased confusion after the titration. [Desipramine](#) serum levels were 1810 ng/mL (therapeutic range 75-300 ng/mL). After decreasing the daily [desipramine](#) 200 mg, the serum [desipramine](#) level was still 1665 ng/mL. The reduction in side effects were evident when the [paroxetine](#) dose was decreased to 30 mg/day and [desipramine](#) dose was decreased to 150 mg/day. Despite the dosage reduction of both drugs the patient's serum [desipramine](#) level was 1153 ng/mL. [Paroxetine](#) was discontinued and [desipramine](#) dose was decreased to 100 mg/day in divided doses. [Citalopram](#) was initiated and titrated to 40 mg/day. Over the next two months the patient's [desipramine](#) level decreased to 195 ng/mL. Depressive symptoms also improved. [Desipramine](#) toxicity is presumed to be caused by hepatic cytochrome P450 2D6 (CYP2D6) isoenzyme blockade from [paroxetine](#). The author concludes that the switch to [citalopram](#) likely is responsible for diminished [desipramine](#) serum levels, although alternative explanations should not be discounted [960].

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

- 1)) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2)) Summary: Tricyclic antidepressants (TCAs) and [clarithromycin](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[600][601]. 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 [clarithromycin](#), is not recommended [602].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concurrent administration of tricyclic antidepressants and agents that prolong the QT interval, such as [clarithromycin](#), is not recommended.
- 7)) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.AU] [Clobazam](#)

- 1)) Interaction Effect: increased [imipramine](#) plasma concentrations
- 2)) Summary: The concomitant use of [imipramine](#), a CYP2D6 substrate[241], and clobazam, a CYP2D6 inhibitor, may increase [imipramine](#) plasma concentrations. Dose reduction of [imipramine](#) may be required when coadministered with clobazam [434]. If clobazam therapy is withdrawn, a higher dose of [imipramine](#) may be necessary [241].
- 3)) Severity: moderate
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of clobazam with [imipramine](#) may cause increased [imipramine](#) plasma concentrations. If concomitant use is required, dose reduction may be warranted for [imipramine](#)[434]. If clobazam therapy is withdrawn, a higher dose of [imipramine](#) may be necessary [241].
- 7)) Probable Mechanism: inhibition of CYP2D6-mediated [imipramine](#) metabolism by clobazam



**3.5.1.AV] Clomipramine**

- 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[241][403].
- 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[241][403].
- 7) Probable Mechanism: additive effects on QT interval prolongation

**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](#)[809]. 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 [810][811][812][813]. Mianserin, a tetracyclic antidepressant, was not shown to exhibit the impairment of [clonidine's](#) antihypertensive effects seen with tricyclic antidepressants [814][815].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response. Higher doses of [clonidine](#) may be required. An alternative class of antihypertensive agents or an alternative class of antidepressants might be considered.
- 7) Probable Mechanism: pharmacological antagonism at central alpha-2 receptors
- 8) Literature Reports

a) The interaction between [clonidine](#) and [desipramine](#) was studied in five hypertensive patients. The results of this double-blind placebo controlled study showed that the introduction of the tricyclic antidepressant led to the loss of blood pressure control in four of the five subjects within two weeks. The rise in the arterial pressure was more prominent in the supine position than in the erect. The average blood pressure increase in the [desipramine](#) period compared to the placebo period was 22/15 mm Hg in the lying position and 12/11 mm Hg standing [806].

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 [807].

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 [808].

### 3.5.1.AX] Clorgyline

- 1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome[322][323][324][325]. Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status [326]. Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely [327][328].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as imipramine with an monoamine oxidase inhibitor (MAOI), such as clorgyline is contraindicated. If imipramine is replacing treatment with clorgyline, a minimum of 2 weeks should elapse after clorgyline is discontinued before therapy with imipramine begins[247]. There is no specific washout period for replacing imipramine treatment with clorgyline. However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with the MAOI [249].
- 7) Probable Mechanism: altered catecholamine uptake and metabolism
- 8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers [247]. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination [304][305][306][307][308][309]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [310].

b) The development of serotonin syndrome due to administration of a TCA after MAOI therapy has been reported. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects [311].

c) A 76-year old woman who had been taking clomipramine 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive

attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [312].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [313].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [314].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranylcypromine](#) in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexial state led to [disseminated intravascular coagulation](#) and eventual death [315].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranylcypromine](#) in any combination, and d) close monitoring of patients [316] [306][307][317][318]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [319]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [319]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [320][307][321].

### 3.5.1.AY] Clozapine

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

2) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), caution is advised when using [clozapine](#) with other drugs that may increase the QT interval, such as [imipramine](#)[383]. If coadministration is required, QT interval monitoring may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), caution is advised when using [clozapine](#) with other drugs that may increase the QT interval, such as [imipramine](#)[383]. If coadministration is required, QT interval monitoring may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

### 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[874], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [875]. The effects of the interaction appear to be estrogen dose-related [876] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [877].
- 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 [865].

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 [866] [867].

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 [868].

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 [869].

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 [870].

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 [871].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [872]. 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 [873].

### 3.5.1.BA] Crizotinib

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

2) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), caution is advised when using crizotinib with other drugs that may increase the QT interval, such as [imipramine](#). If coadministration is required, consider periodically [monitoring ECGs](#) and electrolytes. Treatment with crizotinib should be permanently discontinued in patients who develop grade 4 QTc prolongation and should be withheld in patients who develop grade 3 QTc prolongation until recovery to grade 1 or less, at which time it may be resumed at 200 mg twice daily. If grade 3 QTc prolongation recurs, crizotinib should be withheld until recovery to grade 1 or less and then resumed at 250 mg once daily. If grade 3 QTc prolongation recurs, crizotinib should be permanently discontinued[379].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), caution is advised when using crizotinib with other drugs that may increase the QT interval, such as [imipramine](#). If coadministration is required, consider periodically [monitoring ECGs](#) and electrolytes. Treatment with crizotinib should be permanently discontinued in patients who develop grade 4 QTc prolongation and should be withheld in patients who develop grade 3



QTc prolongation until recovery to grade 1 or less, at which time it may be resumed at 200 mg twice daily. If grade 3 QTc prolongation recurs, crizotinib should be withheld until recovery to grade 1 or less and then resumed at 250 mg once daily. If grade 3 QTc prolongation recurs, crizotinib should be permanently discontinued[379].

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

### 3.5.1.BB| Darifenacin

1J) Interaction Effect: increased [imipramine](#) exposure and potentially increased adverse effects

2J) Summary: Concomitant use of [darifenacin](#) and [imipramine](#) may result in substantially increased exposure to [imipramine](#) and its active metabolite [desipramine](#). The mean maximum concentration (C<sub>max</sub>) and area under the concentration-time curve (AUC) of [imipramine](#) increased 57% and 70%, respectively, when used together with [darifenacin](#) 30 mg once daily at steady-state. Note: The recommended dose of [darifenacin](#) is 7.5 or 15 mg once daily. The AUC of [desipramine](#), the active metabolite of [imipramine](#), increased 3.6-fold. Caution should be used with the coadministration of [darifenacin](#) and CYP2D6 substrates with a narrow therapeutic window, such as tricyclic antidepressants, including [imipramine](#)[546].

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Use caution with the coadministration of [darifenacin](#) and other CYP2D6 substrates with a narrow therapeutic window, such as [imipramine](#). Monitor for [imipramine](#) toxicity.

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

### 3.5.1.BC| Dasatinib

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

2J) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, caution is advised when using [dasatinib](#) with other drugs that may increase the QT interval, such as [imipramine](#)[373]. If coadministration is required, QT interval monitoring may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, caution is advised when using [dasatinib](#) with other drugs that may increase the QT interval, such as [imipramine](#)[373]. If coadministration is required, QT interval monitoring may be warranted.

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

### 3.5.1.BD| Deferasirox

1J) Interaction Effect: increased [imipramine](#) exposure and elimination half-life

2J) Summary: Although the effects of concomitant use of [deferasirox](#) and [imipramine](#) have not been studied, concomitant administration of [deferasirox](#), 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 [deferasirox](#) is coadministered with drugs that are metabolized by CYP1A2, such as [imipramine](#), as a similar reaction can be expected[848]. If [deferasirox](#) and [imipramine](#) are coadministered, monitor for an increase in [imipramine](#) adverse events and/or consider dose modification of [imipramine](#).

3J) Severity: moderate

4J) Onset: unspecified

- 5J) Substantiation: theoretical
- 6J) Clinical Management: Use caution when [deferasirox](#), a CYP1A2 inhibitor, is coadministered with drugs that are metabolized by CYP1A2, such as [imipramine](#)[848]. If [deferasirox](#) and [imipramine](#) are coadministered, monitor for an increase in [imipramine](#) adverse events and/or consider dose modification of [imipramine](#).
- 7J) Probable Mechanism: inhibition of CYP1A2-mediated [imipramine](#) metabolism by [deferasirox](#)

### 3.5.1.BE] [Desipramine](#)

- 1J) Interaction Effect: an increased risk of QT interval prolongation
- 2J) Summary: [Desipramine](#) may prolong the QT interval at very high doses[134], and use with other drugs that may prolong the QT interval, such as [imipramine](#), may result in additive effects on QT interval prolongation. Concomitant use of [desipramine](#) and [imipramine](#) is not common in clinical practice. However, if coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of [desipramine](#) and [imipramine](#) is not common clinical practice. However, if using [desipramine](#) (especially at high doses[134]) and [imipramine](#) concomitantly, use caution due to the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.
- 7J) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.BF] [Desogestrel](#)

- 1J) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic antidepressant toxicity (drowsiness, hypotension, [akathisia](#))
- 2J) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].
- 3J) Severity: minor
- 4J) Onset: delayed
- 5J) Substantiation: probable
- 6J) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7J) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic antidepressant or estrogen inhibition of hepatic microsomal enzymes
- 8J) Literature Reports

aJ) 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 [453].

**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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

**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 [456].

**d)** The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

**e)** The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

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 [459].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.BG| 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](#) [510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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 [501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.BH] [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](#) [510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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 [501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.BII] 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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.BJ] Dextromethorphan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: The concomitant use of [dextromethorphan](#) and a tricyclic antidepressant (such as [imipramine](#)) may result in an increased risk of [serotonin syndrome](#). While not specifically studied with [imipramine](#), 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[826]. If both [imipramine](#) 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 [imipramine](#)), as concomitant use may result in an increased risk of [serotonin syndrome](#)[826].
- 7) Probable Mechanism: additive CNS serotonin concentrations

### 3.5.1.BK] Dicumarol

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[745][746]. Considerable interindividual differences may be found [747].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: In patients receiving oral [anticoagulant therapy](#), the prothrombin time ratio or INR ([international normalized ratio](#)) should be closely monitored with the addition and withdrawal of treatment with [imipramine](#), and should be reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in order to maintain the desired level of [anticoagulation](#).
- 7) Probable Mechanism: decreased dicumarol metabolism; increased dicumarol absorption
- 8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of [nortriptyline](#) or [amitriptyline](#) resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects [742]. 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 [743]. 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 [744]. 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.BL] [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[524], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [525]. The effects of the interaction appear to be estrogen dose-related [526] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [527].

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 [515].

b) A case reported by [516] demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [517].



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 [518].

d) The effect of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [519].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [520].

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 [521].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [522]. 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 [523].

### 3.5.1.BM] Dienogest

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].



- 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 [453].

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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

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 [456].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of

serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

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 [459].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.BN] [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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].
- b)) Human pharmacologic studies have demonstrated that **methylphenidate** may inhibit the metabolism of some tricyclic antidepressants, such as **imipramine**, **clomipramine**, or **desipramine** [505].
- c)) 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 [506][504].
- d)) 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** [507].
- e)) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.BO| **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[556], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [557]. The effects of the interaction appear to be estrogen dose-related [558] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on **estrogen therapy** [559].
- 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 [547].

**b))** A case reported by [548] demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [549].

**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 [550].

**d))** The effect of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [551].

**e))** The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after

taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [552].

**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 [553].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [554]. 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 [555].

### 3.5.1.BP| [Diltiazem](#)

**1)** Interaction Effect: [imipramine](#) toxicity (dry mouth, sedation)

**2)** Summary: [Diltiazem](#) decreased [imipramine](#) oral clearance by 35% (statistically significant) compared to placebo in a randomized, crossover study in 12 healthy subjects[637]. [Diltiazem](#) increased [imipramine](#) bioavailability by 30% compared to placebo which was also significant; the clinical significance of this is not known.

**3)** Severity: minor

**4)** Onset: delayed

**5)** Substantiation: theoretical

**6)** Clinical Management: Monitor for anticholinergic side effects of [imipramine](#) if [diltiazem](#) is added to therapy; lower doses of [imipramine](#) may be appropriate. Conversely, if [diltiazem](#) is discontinued, monitor continued clinical efficacy of [imipramine](#) and adjust dosage accordingly.

**7)** Probable Mechanism: decreased [imipramine](#) clearance

**8)** Literature Reports

**a)** [Imipramine](#) serum concentrations may be altered if administered concomitantly with [diltiazem](#). Following the addition of [imipramine](#) 100 mg/day on day 4 of a 7 day course of [diltiazem](#) 90 mg/q8h during a controlled study, the oral clearance of [imipramine](#) decreased by 35% resulting in a significant increase (35%) in the peak serum concentration. These changes failed to occur when the drug was given to those receiving placebo. Monitor drug levels for effectiveness of [imipramine](#) when adding or decreasing [diltiazem](#) dosages [636].

### 3.5.1.BQ| [Disopyramide](#)

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

**2)** Summary: Concomitant use of tricyclic antidepressants, including [imipramine](#), and class IA antiarrhythmics, including [disopyramide](#), may increase the risk of [cardiotoxicity](#) due to similar cardiac effects of these drugs[282][283]. Therefore, monitoring the patient for signs and symptoms of [cardiac toxicity](#) during coadministration of [disopyramide](#) and [imipramine](#) may be warranted.

**3)** Severity: major

**4)** Onset: unspecified

**5)** Substantiation: theoretical

**6)** Clinical Management: Concomitant use of [disopyramide](#) and [imipramine](#) may increase the risk of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs[282][283]. 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](#) [406].

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

1) Interaction Effect: increased bioavailability of [imipramine](#)

2) Summary: Increased elimination half-life, higher peak plasma levels, and decreased total body clearance of [imipramine](#) when administered during [disulfiram therapy](#) have been demonstrated[761]. The clinical significance of this finding is unknown.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor the patient for excessive adverse effects to [imipramine](#).

7) Probable Mechanism: disulfiram-induced inhibition of [imipramine](#) hepatic metabolism

8) Literature Reports

a) Two healthy men who had been detoxified for 14 days participated in a study to determine the effect of [disulfiram](#) on the pharmacokinetics of [imipramine](#) and [desipramine](#). Doses of [imipramine](#) 12.5 mg were administered intravenously both prior to [disulfiram](#) 500 mg daily therapy and after 14 days of therapy with [disulfiram](#). The protocol for [desipramine](#) was also the same but was performed only in one subject. For [imipramine](#), the area under the concentration-time curve (AUC) increased by 32.5% and 26.8% after [disulfiram](#) administration in patient 1 and patient 2, respectively. The elimination half-lives were also increased by 18.3% and 13.6%, respectively, while the total body [imipramine](#) clearance decreased 24.5% and 21.3%, respectively. [Desipramine](#) showed a 32.3% increase in the AUC when administered with [disulfiram](#). The elimination half-life also increased by 19.8% and the total body clearance decreased 24.3% [761].

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

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

2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including [acecainide](#)[424], [amiodarone](#) [425], [azimilide](#) [426], [bretylium](#) [427], [ibutilide](#) [428], [sotalol](#) [431], [sematilide](#) [429], [dofetilide](#) [430], and [sotalol](#) [431]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [432][433].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical



- 6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports

- a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [422].
- b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetry monitoring is advised [423].

### 3.5.1.BT] [Dolasetron](#)

- 1) Interaction Effect: [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) and [dolasetron](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[275]. 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 [dolasetron](#), is not recommended [276][277].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [dolasetron](#) with other agents that may prolong the QTc interval, such as tricyclic antidepressants, is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

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

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Use caution with coadministration of [imipramine](#), 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 increased risk of sudden cardiac death was observed with the use of oral domperidone, particularly at doses greater than 30 mg/day and in patients older than 60 years of age. If coadministration is necessary, domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure[964].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering domperidone and [imipramine](#) 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[964].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.BV] [Dronedarone](#)

- 1) Interaction Effect: an increased risk of [torsade de pointes](#)



- 2) Summary: Due to the potential for additive effects on the QT interval prolongation and increased risk of [torsade de pointes](#), the concomitant use of dronedarone and [imipramine](#) is contraindicated[816].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of dronedarone and [imipramine](#) is contraindicated due to the potential for additive effects on the QT interval and an increased risk of [torsade de pointes](#)[816].
- 7) Probable Mechanism: additive effects on the QT interval prolongation

### 3.5.1.BW| [Droperidol](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Droperidol](#) has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of [droperidol](#) and other drugs known to prolong the QTc interval, including tricyclic antidepressants is not recommended[879][880].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [droperidol](#) and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.BX| [Drospirenone](#)

- 1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic antidepressant toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].
- 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 [453].

**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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

**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 [456].

**d)** The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

**e)** The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

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 [459].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

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

1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (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[346].

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

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

### 3.5.1.BZ] [Enflurane](#)

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

2) Summary: [Enflurane](#) may prolong the QT interval in some patients[966]. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [enflurane](#) and tricyclic antidepressants is not recommended [967]. Concomitant administration of [amitriptyline](#) and [enflurane anesthesia](#) has been reported to result in seizures in two cases [968].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Two case reports of patients on [amitriptyline](#) therapy who experienced seizure activity while receiving [enflurane anesthesia](#) have been documented [965]. The first patient, a 42-year old female, was taking [amitriptyline](#) 100 mg daily. [Anesthesia](#) was induced with [fentanyl](#), [enflurane](#), and

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

### 3.5.1.CA] [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[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640] 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 [643][644][645][646].
- 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[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640]. 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 [641].

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 [642].

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

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Erythromycin](#) significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients[765]. [Erythromycin](#) has demonstrated QTc prolongation in combination with other

drugs that prolong the QT interval [766]. Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose [767]. Caution is advised with coadministration of drugs that potentially prolong the QTc interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) [Erythromycin](#) did not significantly affect the metabolism of tricyclic antidepressants in a study of 8 patients. Patients were maintained on [desipramine](#) (n equal to 5), [imipramine](#) (n equal to 1), [doxepin](#) (n equal to 1), or [doxepin](#) (n equal to 1). All patients received [erythromycin](#) stearate 250 mg four times daily for six days while maintaining their usual tricyclic regimen. No change in the antidepressant or active metabolite concentrations was seen during coadministration with [erythromycin](#) [762].

b) Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose [763].

c) [Erythromycin](#) significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The [erythromycin](#) dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with [heart disease](#) (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without [heart disease](#) (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed [torsades de pointes](#) attributed to [erythromycin](#). Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater [764].

### 3.5.1.CC] [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[874], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [875]. The effects of the interaction appear to be estrogen dose-related [876] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [877].

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 [865].

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 [866] [867].

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 [868].

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 [869].

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 [870].

**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 [871].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [872]. 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 [873].

### 3.5.1.CD| [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[874], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [875]. The effects of the interaction appear to be estrogen dose-related [876] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [877].

**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 [865].

**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 [866] [867].

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 [868].

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 [869].

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 [870].

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 [871].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [872]. 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 [873].

### 3.5.1.CE] [Estradiol](#) Cypionate

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being

manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].

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 [453].

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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

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 [456].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19

took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

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 [459].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.CF] [Estradiol Valerate](#)

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].

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 [453].

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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

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 [456].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within

hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

**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 [459].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.CG| 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[874], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [875]. The effects of the interaction appear to be estrogen dose-related [876] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [877].

**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 [865].

**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 [866] [867].

**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 [868].

**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 [869].

**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 [870].

**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 [871].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [872]. 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 [873].

### 3.5.1.CH| 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[874], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [875]. The effects of the interaction appear to be estrogen dose-related [876] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [877].
- 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 [865].

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 [866] [867].

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 [868].



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 [869].

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 [870].

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 [871].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [872]. 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 [873].

### 3.5.1.CII [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[874], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [875]. The effects of the interaction appear to be estrogen dose-related [876] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [877].

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 [865].

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 [866] [867].

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 [868].

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 [869].

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 [870].

**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 [871].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [872]. 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 [873].

### 3.5.1.CJ] 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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.CK] Ethinyl Estradiol

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

**2)** Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464]

and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: probable

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

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

8J) Literature Reports

aJ) 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 [453].

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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

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 [456].

dJ) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3

patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

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 [459].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.CL| [Ethinodiol](#) Diacetate

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].

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 [453].

**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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

**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 [456].

**d)** The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

**e)** The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one



week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

**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 [459].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.CM] 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[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640] 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 [643][644][645][646].

**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[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640]. 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 [641].

**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 [642].

**3.5.1.CN] Etonogestrel**

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

**2)** Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].

**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 [453].

**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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

**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 [456].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

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 [459].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.CO] [Fenfluramine](#)

- 1) Interaction Effect: an increased risk of [imipramine](#) toxicity (sedation)
- 2) Summary: When [fenfluramine](#) was added to [imipramine](#) therapy, the blood concentration of [imipramine](#) plus [desipramine](#) was dramatically increased in a 55-year old female. The increased blood levels caused the patient to fall asleep while driving[303].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: If [fenfluramine](#) is used in combination with [imipramine](#), the patient should be monitored for increased sedation, [hypertension](#) and [dysrhythmias](#).
- 7) Probable Mechanism: inhibition of [imipramine](#) metabolism
- 8) Literature Reports

a)) 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 cytochrome p450 isoenzyme responsible for metabolizing [imipramine](#) [301].

b)) A study was conducted in 15 patients with DSM-III [major depression](#) who failed to respond to treatment with [desipramine](#) given for at least four weeks. [Fenfluramine](#) 40 mg to 120 mg daily for two weeks was then added, but led to no transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [302].

### 3.5.1.CP| [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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b)) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c)) 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 [506][504].

d)) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.CQ| Fingolimod

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Fingolimod has been associated with a dose-related prolongation of the QT interval. Concomitant use with other QT interval prolonging agents, such as [imipramine](#), may result in additive QT interval prolongation and should be approached with caution[407]. Monitoring for QT interval prolongation may be warranted during coadministration of fingolimod and [imipramine](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of fingolimod and other drugs that may prolong the QT interval, such as [imipramine](#), should be approached with caution due to the potential for additive effects on QT interval prolongation[407]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive QT interval prolongation

### 3.5.1.CR| Flecainide

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended[773][774][775].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [771].

b) A 68-year-old man suffering from agitated [major depression](#) was begun on a dose of [desipramine](#) 125 mg daily which produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An increased dose of 175 mg daily produced excellent clinical response with no side effects. He developed [atrial fibrillation and flutter](#). [Digoxin](#) 0.25 mg daily was added to his therapy, and [desipramine](#) was discontinued. His [arrhythmia](#) was suppressed with the

addition of propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at which point he experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nmol/L. The desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resumed at 75 mg daily. The desipramine serum level was measured at 1130 nmol/L [772].

### 3.5.1.CS| Fluconazole

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Case reports have described QT prolongation and torsades de points associated with fluconazole[385]. Several tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose [386]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of fluconazole and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.CT| Fluoxetine

- 1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose[839][840]. Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended [841]. In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations [842][842][843][844][845][846].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
- 8) Literature Reports

a) 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 [833].

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 area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three 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 [834].

c) 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 [835].

d) 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 five weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 ng/mL with resolution of clinical symptoms [836].

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 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; eleven 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; the adverse effects resolved in six days. Eight days later, the [desipramine](#) level was 122 ng/mL [837].

f) 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 [838].

### 3.5.1.CU] Fluvoxamine

1) Interaction Effect: [imipramine](#) toxicity (dry mouth, urinary retention, sedation)

2) Summary: Addition of [fluvoxamine](#) to [imipramine](#) or [desipramine](#) therapy can result in significantly increased tricyclic antidepressant plasma levels and signs of tricyclic toxicity[237][238][239]. [Fluvoxamine](#) significantly increases [imipramine](#) half-life and reduces clearance [239]. The addition of [fluvoxamine](#) to [imipramine](#) or [desipramine](#) therapy may result in greatly increased tricyclic antidepressant plasma levels and tricyclic toxicity [237][238]. A bidirectional effect is suggested, in which [fluvoxamine](#) increases [imipramine](#) concentrations (by interfering with N-demethylation), and [imipramine](#) increases [fluvoxamine](#) levels [240].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs of [imipramine](#) and [fluvoxamine](#) toxicity; lower doses of one or both agents may be required with concomitant therapy.

7) Probable Mechanism: decreased [imipramine](#) metabolism

8) Literature Reports

- a) The pharmacokinetics of combined **imipramine** and **fluvoxamine** were studied in healthy volunteers [233]. After a 7-day course of **fluvoxamine**, **imipramine** half-life was significantly increased (from 23 to 41 hours) and clearance decreased (from 1.02 to 0.28 L/h/kg).
- b) The addition of **fluvoxamine** to **imipramine** or **desipramine** in four patients was reported to result in greatly increased tricyclic antidepressant plasma levels [234]. Three of four patients showed signs of tricyclic toxicity. The effect of **fluvoxamine** 100 mg daily for 10 days on plasma concentrations of **imipramine** was studied in seven depressed patients on maintenance therapy [235]. **Imipramine** plasma levels were three to four times higher during **fluvoxamine** coadministration. One patient complained of anticholinergic effects, along with tremor and confusion. The mechanism of this drug interaction was inhibition of demethylation of **imipramine**. A **pharmacokinetic study** in healthy volunteers demonstrated a significantly increased **imipramine** half-life and reduced clearance [233].
- c) Metabolism of tricyclic antidepressants coadministered with **fluvoxamine** was studied in eight depressed patients (two patients received **imipramine**) [236]. **Fluvoxamine** was found to interfere with N-demethylation of **imipramine**. The combination of **fluvoxamine** and **imipramine** led to increased plasma levels of **imipramine** and decreased concentrations of the N-demethylated **imipramine** metabolite desimipramine. In addition, TCA-fluvoxamine coadministration apparently raised plasma levels of **fluvoxamine**.

### 3.5.1.CV] **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[649]. 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[649].
- 7) Probable Mechanism: potentiation of cardiovascular effects

### 3.5.1.CW] **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**[603].
- 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)[603].

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

### 3.5.1.CX] Foscarnet

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

2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and tricyclic antidepressants is not recommended[881][882].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of foscarnet and tricyclic antidepressants is not recommended.

7) Probable Mechanism: additive cardiac effects

### 3.5.1.CY] Fosphenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)

2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin[690]. A few case reports have indicated that imipramine inhibits phenytoin metabolism resulting in increased serum phenytoin concentration [691][692]. 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 monitoring phenytoin serum levels if a tricyclic antidepressant is added to therapy or if the patient begins to exhibit signs of toxicity (tremor, nystagmus, ataxia, hyperreflexia); 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.CZ] 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[827].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

- 6J) Clinical Management: The concurrent administration of [gatifloxacin](#) and a tricyclic antidepressant is not recommended.
- 7J) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.DA| Gemifloxacin

- 1J) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2J) Summary: Although [pharmacokinetic studies](#) between gemifloxacin and drugs that prolong the QT interval, such as tricyclic antidepressants, have not been performed, gemifloxacin should be used cautiously when given concurrently with tricyclic antidepressants[770].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as gemifloxacin and tricyclic antidepressants, is not recommended.
- 7J) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.DB| Granisetron

- 1J) Interaction Effect: an increased risk of QT interval prolongation
- 2J) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, caution is advised when using [granisetron](#) with other drugs that may increase the QT interval, such as [imipramine](#)[395]. If coadministration is required, QT interval monitoring may be warranted.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, caution is advised when using [granisetron](#) with other drugs that may increase the QT interval, such as [imipramine](#)[395]. If coadministration is required, QT interval monitoring may be warranted.
- 7J) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.DC| Grepafloxacin

- 1J) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2J) 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[591].
- 3J) Severity: contraindicated
- 4J) Onset: delayed
- 5J) Substantiation: probable
- 6J) 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.
- 7J) Probable Mechanism: additive cardiac effects

**3.5.1.DD] 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[828][829]. 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 [830].
- 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 angiotensin-converting enzyme inhibitors might be considered.
- 7) Probable Mechanism: decreased uptake of [guanadrel](#) into adrenergic neurons

**3.5.1.DE] Guanethidine**

- 1) Interaction Effect: decreased antihypertensive effectiveness
- 2) Summary: Tricyclic antidepressants inhibit the uptake of [guanethidine](#), and possibly [guanadrel](#), into the adrenergic neuron, resulting in an inhibition of the antihypertensive effect[802][803][804][805].
- 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 [guanethidine](#) may be required. An alternative class of antihypertensive agents, such as angiotensin-converting enzyme inhibitor might be considered.
- 7) Probable Mechanism: decrease uptake of [guanethidine](#) into adrenergic neurons

**3.5.1.DF] Guanfacine**

- 1) Interaction Effect: decreased antihypertensive effectiveness
- 2) Summary: Concomitant [clonidine](#) and tricyclic antidepressant (TCA) therapy may impair the antihypertensive effects of [clonidine](#). Since the mechanism of action of [guanfacine](#) is similar to [clonidine](#), patients stabilized on [guanfacine](#) should be monitored for a hypertensive response when TCA (i.e. [desipramine](#) or [imipramine](#)) therapy is started[754][755]. A case has been reported of a patient maintained on [guanfacine](#) who developed an increase in blood pressure when [imipramine](#) was added to therapy. When [imipramine](#) was discontinued, her blood pressure returned to baseline [756].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher doses of [guanfacine](#) may be required. An alternative class of antihypertensive agents, such as an angiotensin-converting enzyme inhibitor might be considered.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A case of a hypertensive female who was maintained on [guanfacine](#) 2 mg daily with mean blood pressure at 138/89 mm Hg was reported [751]. After [amitriptyline](#) 75 mg daily was begun, her mean blood pressure was 150/100 mm Hg; upon discontinuation of the [amitriptyline](#), the blood pressure returned to 136/91 mm Hg. A month later she was given [imipramine](#) 50 mg daily and experienced

similar changes in loss of blood pressure control; upon discontinuation of [imipramine](#), the blood pressure again returned to 137/90 mm Hg.

**b))** Concomitant [clonidine](#) and tricyclic antidepressant therapy may impair the antihypertensive effects of [clonidine](#). Since the mechanism of action of [guanfacine](#) is similar to [clonidine](#), patients stabilized on [guanfacine](#) should be monitored for a hypertensive response when [desipramine](#) therapy is started [752][753].

### 3.5.1.DG| [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[280][281].

**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.DH| [Haloperidol](#)

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

**2))** Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride[334], [haloperidol](#) [335], [risperidone](#) [336], sertindole [337], [quetiapine](#) [338], sultopride [339], and zotepine [340]. Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended [341][342].

**3))** Severity: major

**4))** Onset: unspecified

**5))** Substantiation: theoretical

**6))** Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

**7))** Probable Mechanism: additive cardiac effects

**8))** Literature Reports

**a))** Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [333].

### 3.5.1.DI| [Halothane](#)

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



2) Summary: [Halothane](#) may prolong the QT interval in some patients[544]. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [halothane](#) and tricyclic antidepressants is not recommended [545].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of [halothane](#) and tricyclic antidepressants is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.DJ] 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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.DK] 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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.DL] [Ibutilide](#)

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

2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[424], [amiodarone](#) [425], azimilide [426], [bretium](#) [427], [ibutilide](#) [428], sotalol [429], [dofetilide](#) [430], and [sotalol](#) [431]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [432][433].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [422].

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetry monitoring is advised [423].

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

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

2) Summary: The concomitant use of iloperidone with other drugs that may cause QT interval prolongation, such as [imipramine](#), should be avoided due to an increased risk of QT interval prolongation and [torsade de pointes](#)[391].

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of iloperidone with other drugs that may cause QT interval prolongation, such as [imipramine](#), should be avoided due to an increased risk of QT interval prolongation and [torsade de pointes](#)[391].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.DN] 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](#)[768].
- 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](#)[768].
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.DO] Iobenguane I 131

- 1) Interaction Effect: false-negative results of [scintigraphy](#)
- 2) Summary: [Imipramine](#), which selectively blocks the active transport of catecholamines into storage vesicles, reduces myocardial uptake of [iobenguane I-131](#) and increases the rate of loss of [iobenguane I-131](#) from the liver, thus interfering with [scintigraphy](#)[242].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: [Imipramine](#) should be discontinued prior to any procedure using [iobenguane I-131](#).
- 7) Probable Mechanism: reduction of [iobenguane I-131](#) uptake

### 3.5.1.DP] Iproniazid

- 1) Interaction Effect: [neurotoxicity](#), seizures, or [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[931][932][933][934]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [935]. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#), and monitor patients closely [936][937].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the

potential risk. Other antidepressant therapy should first be considered. Consider using a 14 day washout period between treatment with both medicines. If deemed clinically necessary, avoid large doses and use agents other than [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#).

7) Probable Mechanism: altered catecholamine uptake and metabolism

#### 8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [920][921][922][923]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [924].

b) Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [925].

c) A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [926].

d) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranylcypromine](#) in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexial state led to [disseminated intravascular coagulation](#) and eventual death [927].

e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [928]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [929][922][930].

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

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

2) Summary: The concurrent administration of [isocarboxazid](#) and [imipramine](#) is contraindicated[794]. Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#) [795][796][797][798]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation

characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [799]. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranlycypromine](#), and monitor patients closely [800][801].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOI) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [776][777][778][779][780][781]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [782].

b) The development of [serotonin syndrome](#) was reported due to administration of a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [783].

c) A drug interaction was reported when a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [784].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [785].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs

and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [786].

**f)** In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranylcypromine](#) in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexial state led to [disseminated intravascular coagulation](#) and eventual death [787].

**g)** There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranylcypromine](#) in any combination, and d) close monitoring of patients [788] [778][779][789][790]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [791]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [791]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [792][779][793].

### 3.5.1.DR| [Isoflurane](#)

- 1)** Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2)** Summary: [Isoflurane](#) may prolong the QT interval in some patients[970]. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [isoflurane](#) and tricyclic antidepressants is not recommended [971].
- 3)** Severity: major
- 4)** Onset: unspecified
- 5)** Substantiation: theoretical
- 6)** Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of [isoflurane](#) and a tricyclic antidepressant is not recommended.
- 7)** Probable Mechanism: additive effect on QT prolongation

### 3.5.1.DS| [Isradipine](#)

- 1)** Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2)** Summary: [Isradipine](#) can prolong the QT interval in some patients, which may result in [ventricular tachycardia](#), [ventricular fibrillation](#), and [torsades de pointes](#). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [isradipine](#) with a tricyclic antidepressant is not recommended[955][956].
- 3)** Severity: major
- 4)** Onset: unspecified
- 5)** Substantiation: theoretical
- 6)** Clinical Management: The concurrent administration of [isradipine](#) and a tricyclic antidepressant is not recommended.
- 7)** Probable Mechanism: additive cardiac effects



**3.5.1.DT] Ketoconazole**

- 1) Interaction Effect: decreased clearance and prolonged half-life of **imipramine**
- 2) Summary: In a controlled study of six healthy volunteers, coadministration of **ketoconazole** with a single dose of **imipramine** resulted in an increase in **imipramine** area under the concentration-time curve (AUC) and **imipramine** half-life as well as a decrease in **imipramine** clearance. The changes were minor, however, and deemed to be likely clinically insignificant considering the wide therapeutic range of **imipramine**[973].
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, downward dosage adjustments of **imipramine** may be necessary.
- 7) Probable Mechanism: inhibition of **imipramine** hepatic metabolism
- 8) Literature Reports

a) A controlled study evaluated oral **ketoconazole** and the pharmacokinetic effects on oral **imipramine** and **desipramine** in 12 healthy male volunteers. The subjects were divided into two groups and received either a single dose of **imipramine** 100 mg or **desipramine** 100 mg, both alone and after 10 days of a 14-day regimen of oral **ketoconazole** 200 mg per day. Coadministration of **ketoconazole** resulted in significantly increased **imipramine** area under the concentration-time curve (AUC) values (from 3795 +/- 918 nmol h/L to 4567 +/- 1076 nmol h/L) and significantly decreased **imipramine** oral clearance (from 1.16 +/- 0.21 L/hr/kg to 0.96 +/- 0.20 L/hr/kg). **Imipramine** half-life was also significantly increased during coadministration with **ketoconazole**, from 16.7 +/- 3.3 hours to 19.2 +/- 5.4 hours. The changes in **imipramine** pharmacokinetics were deemed to be minor considering the therapeutic range of the drug. During coadministration of **ketoconazole** with **desipramine**, no significant pharmacokinetic changes were observed. The authors concluded that **ketoconazole** inhibits the N-demethylation of **imipramine** by cytochrome P450 3A4, without affecting the 2-hydroxylation of **imipramine** and **desipramine**, which is thought to be mediated through the cytochrome P450 2D6 pathway [972].

**3.5.1.DU] Labetalol**

- 1) Interaction Effect: **imipramine** toxicity (dry mouth, urinary retention, sedation)
- 2) Summary: **Labetalol** decreased **imipramine** clearance by 38% (statistically significant) compared to placebo in a randomized, crossover study in 12 healthy subjects[647]. **Labetalol** increased **imipramine** area under the concentration-time curve (AUC) by 53% compared to placebo, which was also significant. The clinical significance of the pharmacokinetic interaction is undetermined.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for anticholinergic side effects of **imipramine** if **labetalol** is added to therapy; lower doses of **imipramine** may be appropriate. Conversely, if **labetalol** is discontinued, monitor continued clinical efficacy of **imipramine** and adjust dosage accordingly.
- 7) Probable Mechanism: decreased **imipramine** metabolism, increased **imipramine** AUC

**3.5.1.DV] Lapatinib**

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

2)) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, caution is advised when using lapatinib with other drugs that may increase the QT interval, such as [imipramine](#). If coadministration is required, consider [monitoring ECGs](#) and electrolytes[389].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, caution is advised when using lapatinib with other drugs that may increase the QT interval, such as [imipramine](#). If coadministration is required, consider [monitoring ECGs](#) and electrolytes[389].

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

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

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

2)) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), concomitant use of [levofloxacin](#) with other drugs that may increase the QT interval, such as [imipramine](#), should be used with caution. Additionally elderly patients may be particularly sensitive to QT prolongation associated with drug effects, take appropriate precautions when coadministering these drugs to this patient population[723]. If coadministration is required, QT interval monitoring may be warranted.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), concomitant use of [levofloxacin](#) with other drugs that may increase the QT interval, such as [imipramine](#), should be used with caution. Additionally elderly patients may be particularly sensitive to QT prolongation associated with drug effects, take appropriate precautions when coadministering these drugs to this patient population[723]. If coadministration is required, QT interval monitoring may be warranted.

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

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

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

2)) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as [imipramine](#) that prolong the QT interval[381].

3)) Severity: contraindicated

4)) Onset: delayed

5)) Substantiation: theoretical

6)) Clinical Management: Levomethadyl is contraindicated in patients being treated with [imipramine](#) as it may precipitate QT prolongation and interact with levomethadyl.

7)) Probable Mechanism: unknown

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

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

2j) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].

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 [453].

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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

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 [456].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

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 [459].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.DZ] Lidoflazine

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

2) Summary: Tricyclic antidepressants (TCAs) and lidoflazine have been shown to prolong the QTc interval at the recommended therapeutic dose[758][759]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as lidoflazine, is not recommended [760].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of lidoflazine and tricyclic antidepressants is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.EA] [Linezolid](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hyperthermia](#), hyperreflexia, myoclonus, mental status changes)
- 2) Summary: Concomitant use of [linezolid](#) and a tricyclic antidepressant, such as [imipramine](#), is contraindicated in the absence of monitoring for [serotonin syndrome](#). If symptoms occur, consider discontinuation of either one or both of the drugs. [Linezolid](#) is a reversible, nonselective inhibitor of monoamine oxidase and may therefore interact with tricyclic antidepressants. Spontaneous reports of [serotonin syndrome](#) associated with the co-administration of [linezolid](#) and serotonergic agents have been reported[729].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [linezolid](#) and tricyclic antidepressants, such as [imipramine](#), is contraindicated unless patient is closely observed for signs and/or symptoms of [serotonin syndrome](#). If concomitant use is clinically warranted, monitor for signs and symptoms of [serotonin syndrome](#), such as neuromuscular abnormalities (including 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[378][729].
- 7) Probable Mechanism: additive serotonergic effects
- 8) Literature Reports

a) A case report described [serotonin syndrome](#) in a 36-year-old woman following the concomitant use of [linezolid](#) and [imipramine](#). The patient, who had no history of seizures and whose regimen included [lithium](#), [venlafaxine](#), and [imipramine](#) for [bipolar disorder](#), [depression](#), and headaches, respectively, presented to the emergency room (ER) with seizures. Ten days prior to presenting to the ER, the patient received [vancomycin](#) for treatment of MRSA empyema. However, therapy was switched to [linezolid](#) approximately 36 hours before her ER visit. At presentation, she had a blood pressure (BP) of 234/196 mmHg, a heart rate of 160 beats/min, respiratory rate of 24 breaths/min, and diaphoresis. Her pupils were dilated with slow reaction to light and she was unresponsive to verbal instructions. The patient was intubated and administered multiple doses of [lorazepam](#), which lessened her tremors and decreased BP to 150/85 mmHg. Her serum [lithium](#) level was 1.2 mEq/L and there were no electrolyte abnormalities. Within 3 hours of intubation, mental status and breathing pattern normalized and the patient was extubated. While both [imipramine](#) and [venlafaxine](#) were withheld, [lithium](#) was continued and [linezolid](#) was replaced with [trimethoprim](#) and [sulfamethoxazole](#). The patient remained alert and oriented over the following days and had reduced anxiety. Three weeks following discharge, the patient reported tremors and anxiety after reinstituting [venlafaxine](#) and [imipramine](#). It was postulated that her 3 chronic serotonergic medications led to a baseline hyperserotonergic state, which was acutely aggravated by the addition of [linezolid](#) [730].

### 3.5.1.EB] Lisdexamfetamine

- 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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine

tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.EC] Lorcaïnide

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

2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended[773][774][775].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical



- 6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [771].

b) A 68-year-old man suffering from agitated [major depression](#) was begun on a dose of [desipramine](#) 125 mg daily which produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An increased dose of 175 mg daily produced excellent clinical response with no side effects. He developed [atrial fibrillation and flutter](#). [Digoxin](#) 0.25 mg daily was added to his therapy, and [desipramine](#) was discontinued. His [arrhythmia](#) was suppressed with the addition of [propafenone](#) 150 mg twice daily and 300 mg at bedtime. [Desipramine](#) 150 mg daily was again begun, at which point he experienced dry mouth, sedation, and shakiness; the [desipramine](#) serum level was measured at 2092 nmol/L. The [desipramine](#) was discontinued for five days, the side effects ceased, and [desipramine](#) therapy was resumed at 75 mg daily. The [desipramine](#) serum level was measured at 1130 nmol/L [772].

### 3.5.1.ED] Lorcaserin

- 1) Interaction Effect: increased [imipramine](#) plasma concentrations; increased risk of [serotonin syndrome](#)
- 2) Summary: The concomitant use of [imipramine](#), a CYP2D6 substrate[421], and lorcaserin, a CYP2D6 inhibitor, may cause increased [imipramine](#) plasma concentrations resulting in increased [imipramine](#) adverse effects. Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic neurotransmitter system, such as [imipramine](#), may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution [420]. Dose reduction of [imipramine](#) may be required when coadministered with lorcaserin, and if lorcaserin therapy is withdrawn, a higher dose of [imipramine](#) may be necessary. [Imipramine](#) plasma level monitoring may be desirable with coadministration [421].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution with the concomitant use of [imipramine](#) with lorcaserin as this may cause increased [imipramine](#) plasma concentrations and may also result in additive serotonergic effects, increasing the risk of [serotonin syndrome](#)[420]. If concomitant use is required, dose reduction may be warranted for [imipramine](#). If lorcaserin therapy is withdrawn, a higher dose of [imipramine](#) may be necessary. [Imipramine](#) plasma level monitoring may be desirable with coadministration [421].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [imipramine](#) metabolism by lorcaserin; additive serotonergic effects

### 3.5.1.EE] Lumefantrine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Lumefantrine is a CYP2D6 inhibitor and may cause QT interval prolongation. Concomitant use of artemether/lumefantrine and a CYP2D6 substrate (eg, [amitriptyline](#), [clomipramine](#), [flecainide](#), and [imipramine](#)) can lead to elevated drug levels of the CYP2D6 substrate. As some CYP2D6 substrates can also prolong the QT interval, there is potential for additive QT prolongation. Therefore, artemether/lumefantrine should not be coadministered with CYP2D6 substrates that possess cardiac effects[680].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Artemether/lumefantrine should not be administered concomitantly with CYP2D6 substrates, such as [amitriptyline](#), [clomipramine](#), [flecainide](#), and [imipramine](#), due to the potential additive effect on QT interval prolongation[680].
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.EF] [Mazindol](#)

- 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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.EG] **Medroxyprogesterone Acetate**

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on **estrogen therapy** [465].

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 [453].

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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

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 [456].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

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 [459].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.EH] [Mefloquine](#)

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

2) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, caution is advised when using [mefloquine](#) with other drugs that may increase the QT interval, such as [imipramine](#)[724]. If coadministration is required, QT interval monitoring may be warranted.

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, caution is advised when using [mefloquine](#) with other drugs that may increase the QT interval, such as [imipramine](#)[724]. If coadministration is required, QT interval monitoring may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.EI] [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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.EJ] Mephobarbital

- 1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
- 2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.EK] Mesoridazine

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Although citing no data, the manufacturer of [mesoridazine](#) states that concomitant use with other drugs which prolong the QT interval is contraindicated[668]. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation [669].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of a tricyclic antidepressant and [mesoridazine](#) is contraindicated.
- 7) Probable Mechanism: additive effect on QT interval

### 3.5.1.EL] Mestranol



- 1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic antidepressant toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].
- 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 [453].

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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

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 [456].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

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 [459].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.EMJ [Methadone](#)

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

2) Summary: Caution is advised with the concomitant use of [methadone](#) and other QT prolonging drugs, such as [imipramine](#), as this may result in additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsade de pointes](#). If concomitant therapy is required, monitor cardiovascular status for QT prolongation or [dysrhythmias](#)[687].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised with the concomitant use of [methadone](#) and other QT prolonging drugs, such as [imipramine](#), as this may result in additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsade de pointes](#). If concomitant therapy is required, monitor cardiovascular status for QT prolongation or [dysrhythmias](#)[687].

7) Probable Mechanism: additive effects on QT interval prolongation

**3.5.1.EN] 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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

**3.5.1.EO] 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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.EP] [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[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640] 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 [643][644][645][646].
- 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[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640]. 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 [641].

**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 [642].

### 3.5.1.EQ] Methylene Blue

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

**2)** Summary: Concurrent use of [imipramine](#) and methylene blue (an MAOI) is contraindicated[241]. Concurrent administration may result in potentially fatal [serotonin syndrome](#) [343]. In settings where urgent treatment with methylene blue is not required, discontinue [imipramine](#) at least 14 days prior to initiating treatment with methylene blue. If no alternative pharmacological or non-pharmacological treatment is available and urgent treatment with methylene blue is required in a patient on [imipramine](#) therapy, and the potential benefits outweigh the risk of [serotonin syndrome](#), [imipramine](#) must be discontinued immediately. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. [Imipramine](#) may be resumed 24 hours after the last dose of methylene blue has been given [344].

**3)** Severity: contraindicated

**4)** Onset: unspecified

**5)** Substantiation: probable

**6)** Clinical Management: Concurrent use of [imipramine](#) and methylene blue (an MAOI) is contraindicated[241]. Concurrent administration may result in potentially fatal [serotonin syndrome](#) [343]. In settings where urgent treatment with methylene blue is not required, discontinue [imipramine](#) at least 14 days prior to initiating treatment with methylene blue. If no alternative pharmacological or non-pharmacological treatment is available and urgent treatment with methylene blue is required in a patient on [imipramine](#) therapy, and the potential benefits outweigh the risk of [serotonin syndrome](#), [imipramine](#) must be discontinued immediately. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. [Imipramine](#) may be resumed 24 hours after the last dose of methylene blue has been given [344].

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

### 3.5.1.ER] Methylphenidate

**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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.ES] [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[231]. 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 [232].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of tricyclic antidepressant with [metoclopramide](#) is contraindicated[231]. 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 [232].

7J) Probable Mechanism: unknown

### 3.5.1.ETJ [Mibefradil](#)

1J) Interaction Effect: an increased risk of [imipramine](#) toxicity (drowsiness, hypotension, [akathisia](#))

2J) Summary: Imipramine is metabolized by cytochrome P450 2D6 and has a high first-pass effect. When [mibefradil](#) (an inhibitor of CYP450 2D6) and [imipramine](#) were coadministered, the area under the concentration-time curve (AUC) of [imipramine](#) was increased seven- to eight-fold[731].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Monitor patients for excessive [imipramine](#) adverse effects (drowsiness, hypotension, [akathisia](#)). A dosage adjustment of [imipramine](#) may be necessary.

7J) Probable Mechanism: inhibition of [imipramine](#) metabolism

### 3.5.1.EUJ [Midodrine](#)

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

2J) Summary: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640] 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 [643][644][645][646].

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: Concomitant use of local anesthetic solutions containing [epinephrine](#) to patients receiving a tricyclic antidepressant may produce severe, prolonged [hypertension](#) and should be avoided. If concurrent therapy is necessary, patients should be closely monitored[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640]. 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 [641].

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 [642].

### 3.5.1.EV] Mifepristone

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Mifepristone](#) can prolong the QT interval in a dose-dependent manner. The concomitant use of [mifepristone](#) (Korlym(TM)) with other drugs that may prolong the QT interval, such as [imipramine](#), should be avoided as it may result in additive QT interval prolongation. Due to the long half-life of [mifepristone](#), wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before initiating [imipramine](#). However, if concomitant use is necessary, use the lowest effective dose possible and monitor closely for QT interval prolongation; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing the [imipramine](#) dose[832].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the concomitant use of [imipramine](#) and [mifepristone](#) due to the potential for 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 [mifepristone](#). However, if concomitant use is necessary, use the lowest effective dose possible and monitor closely for QT interval prolongation; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing the [mifepristone](#) dose[832].
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.EW] Mirabegron

- 1) Interaction Effect: increased [imipramine](#) exposure
- 2) Summary: Patients concurrently treated with mirabegron, a moderate CYP2D6 inhibitor[969], and [imipramine](#), a CYP2D6 substrate [421], may have an increase in [imipramine](#) 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 [421].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of mirabegron, a moderate CYP2D6 inhibitor[969], and [imipramine](#), a CYP2D6 substrate [421], may result in increased [imipramine](#) 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 [421].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [imipramine](#) metabolism by mirabegron

### 3.5.1.EX] Moclobemide

- 1) Interaction Effect: [neurotoxicity](#), seizures, or [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[268][269][270][271]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [272]. Subsequently, the concomitant use of TCAs and MAOIs is contraindicated in most cases. If

TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#), and monitor patients closely [273][274].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Concomitant use of moclobemide and [imipramine](#) is contraindicated. If [imipramine](#) is replacing treatment with moclobemide, a minimum of 2 weeks should elapse after moclobemide is discontinued and [imipramine](#) therapy is begun[247]. However, the manufacturer of moclobemide recommends a short washout period of 2 days after discontinuation of moclobemide and before [imipramine](#) is initiated [248]. There is no specific washout period for replacing [imipramine](#) treatment with moclobemide. However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with an MAOI [249].

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [247][250][251][252][253][254][255]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [256].

b) A clinical study designed to detect an interaction between moclobemide and a tricyclic antidepressant ([clomipramine](#)) resulted in severe adverse effects, and the study was terminated. Information about interactions with moclobemide and other tricyclic antidepressants is limited [248].

c) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [257].

d) A drug interaction occurred in which a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [258].

e) A clinical study designed to detect an interaction between moclobemide and a tricyclic antidepressant ([clomipramine](#)) resulted in severe adverse effects, and the study was terminated. Information about interactions with moclobemide and other tricyclic antidepressants is limited [248].

f) Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions

characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [259].

g) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [260].

h) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranlycypromine](#) in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to [disseminated intravascular coagulation](#) and eventual death [261].

i) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranlycypromine](#) in any combination, and d) close monitoring of patients [262][252][253][263][264]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [265]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [265]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [266][253][267].

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

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

2) Summary: Concomitant use of tricyclic antidepressants, including [imipramine](#), and class IA antiarrhythmics, including [morcizine](#), may increase the risk of [cardiotoxicity](#) due to similar cardiac effects of these drugs[282][283]. Therefore, monitoring the patient for signs and symptoms of [cardiac toxicity](#) during coadministration of [imipramine](#) and [morcizine](#) may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [imipramine](#) and [morcizine](#) may increase the risk of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs[282][283]. 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 [406].

### 3.5.1.EZ] Moxifloxacin

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Moxifloxacin has been shown to prolong the QT interval in some patients and should be avoided in those patients receiving agents that also prolong the QT interval, such as tricyclic antidepressants. Although pharmacokinetic studies between moxifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, moxifloxacin should be used with caution when given concurrently with a tricyclic antidepressant[397].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Moxifloxacin should be used with caution when given concurrently with a tricyclic antidepressant.
- 7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.FA] 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[230].
- 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.FB] Nialamide

- 1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome[913][914][915][916]. Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status [917]. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely [918][919].
- 3) Severity: major

- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#).
- 7) Probable Mechanism: altered catecholamine uptake and metabolism
- 8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [902][903][904][905]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [906].

b) In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [907].

c) A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [908].

d) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranylcypromine](#) in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexial state led to [disseminated intravascular coagulation](#) and eventual death [909].

e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [910]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [911][904][912].

### 3.5.1.FC] Nilotinib

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), concomitant use of nilotinib with other drugs that may increase the QT interval,



such as [imipramine](#), should be avoided[688]. If coadministration is required, QT interval monitoring may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), concomitant use of nilotinib with other drugs that may increase the QT interval, such as [imipramine](#), should be avoided[688]. If coadministration is required, QT interval monitoring may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

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

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].

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 [453].

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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

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 [456].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

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 [459].

g) Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

### 3.5.1.FE] [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[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640]. 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 [643][644][645][646].

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[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640]. 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 [641].

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 [642].

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

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].

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 [453].

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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

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 [456].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within

hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

**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 [459].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

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

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

**2)** Summary: Concomitant use of [norfloxacin](#) and other QT prolonging drugs, such as [imipramine](#), may increase the risk of QT interval prolongation and serious cardiovascular effects and should be undertaken with caution. Geriatric patients may be particularly sensitive to QT prolongation[443]. 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 [imipramine](#) 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[443]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.

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

### 3.5.1.FH] [Norgestimate](#)

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

**2)** Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].

**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



## 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 [453].

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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

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 [456].

d) The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#)



1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

**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 [459].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

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

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

**2)** Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[462], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [463]. The effects of the interaction appear to be estrogen dose-related [464] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [465].

**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 [453].

**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 [454]. Some investigators have proposed that the side effects resulted from enhanced tricyclic antidepressant effects secondary to estrogen inhibition of hepatic microsomal enzymes [455].

**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 [456].

**d)** The effects of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40 years. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 patients in the control group (2 due to side effects) and 5 in the experimental group (2 due to side effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [457].

**e)** The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [458].

**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 [459].

**g)** Estrogens may inhibit the oxidation of tricyclic antidepressants (TCAs) by affecting hepatic microsomal enzymes [460]. 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 [461].

#### 3.5.1.FJ] Nortriptyline

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [nortriptyline](#) and [imipramine](#) is not common clinical practice. However, if using [nortriptyline](#) and [imipramine](#) 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 [nortriptyline](#) and [imipramine](#) is not common clinical practice. However, if using [nortriptyline](#) and [imipramine](#) 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.FK] Octreotide

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) and [octreotide](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[444][445]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [octreotide](#), is not recommended [446].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [octreotide](#) and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

#### 3.5.1.FL] Ofloxacin

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [ofloxacin](#) and [imipramine](#) may increase the risk of QT interval prolongation and serious cardiovascular effects and should be undertaken with caution. Because geriatric patients may be particularly sensitive to QT prolongation associated with drug effects, appropriate precautions should be taken when coadministering these drugs to this patient population[847]. 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 [imipramine](#) and [ofloxacin](#) may increase the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects and should be undertaken with caution. Because geriatric patients may be particularly sensitive to QT prolongation associated with drug effects, take appropriate precautions when coadministering these drugs to this patient population[847]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.FM] 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[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640] 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 [643][644][645][646].
- 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[639]. The effects of [epinephrine](#) may be potentiated by tricyclic antidepressants [640]. 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 [641].

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 [642].

**3.5.1.FN] Paliperidone**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), concomitant use of [paliperidone](#) with other drugs that may increase the QT interval, such as [imipramine](#), should be avoided[704]. If coadministration is required, QT interval monitoring may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), concomitant use of [paliperidone](#) with other drugs that may increase the QT interval, such as [imipramine](#), should be avoided[704]. If coadministration is required, QT interval monitoring may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.FO] Pargyline

- 1) Interaction Effect: [neurotoxicity](#), seizures, or [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[895][896][897][898]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), [myoclonus](#), and changes in mental status [899]. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#), and monitor patients closely [900][901].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#).
- 7) Probable Mechanism: altered catecholamine uptake and metabolism
- 8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [883][884][885][886]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [887].

b) Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [888].

c) A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [889].

d) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranylcypromine](#) in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to [disseminated intravascular coagulation](#) and eventual death [890].

e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [891]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added [892]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [893][885][894].

### 3.5.1.FP] Paroxetine

- 1) Interaction Effect: [imipramine](#) toxicity (dry mouth, sedation, urinary retention)
- 2) Summary: [Paroxetine](#) coadministered with [desipramine](#) or [imipramine](#) produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients[295][296][297]. [Paroxetine's](#) effect on TCAs may resemble that of [fluoxetine](#) (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism [298][299][300]. With coadministration, monitor patients for [imipramine](#) toxicity. [Imipramine](#) doses may need to be reduced.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of [paroxetine](#) with other drugs that are metabolized by cytochrome P450 2D6 (CYP2D6) should be approached with caution. When [paroxetine](#) is coadministered with [imipramine](#), monitor patients for signs and symptoms of [imipramine](#) toxicity (dry mouth, sedation, urinary retention, blurred vision). [Imipramine](#) doses may need to be reduced.
- 7) Probable Mechanism: decreased cytochrome P450 2D6-mediated [imipramine](#) metabolism
- 8) Literature Reports

a) The effect of [paroxetine](#) on [desipramine](#) metabolism was studied in nine extensive metabolizers (EM) and eight poor metabolizers (PM) of [desipramine](#). Subjects took a single oral dose of [desipramine](#) before starting [paroxetine](#) and a second dose after 11 days of [paroxetine](#) use. After the addition of [paroxetine](#), EMs experienced a 5-fold decrease in clearance of [desipramine](#), indicating that [paroxetine](#) inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of [desipramine](#) with [paroxetine](#). With concurrent administration of [desipramine](#) and [paroxetine](#), interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of [desipramine](#) [294].

### 3.5.1.FQ] Pazopanib

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), caution is advised when using pazopanib with other drugs that may increase the QT interval, such as [imipramine](#). If coadministration is required, consider [monitoring ECGs](#) and electrolytes[706].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), caution is advised when using pazopanib with other drugs that may increase the QT interval, such as [imipramine](#). If coadministration is required, consider [monitoring ECGs](#) and electrolytes[706].
- 7) Probable Mechanism: additive effects on QT interval prolongation



**3.5.1.FR] 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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

**3.5.1.FS] Pentamidine**

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) and [pentamidine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[701][702]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [pentamidine](#), is not recommended [703].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [pentamidine](#) and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.FT] [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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma [desipramine](#) concentrations (74 nmol/L vs. 107 nmol/L), smaller [desipramine](#) area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter [desipramine](#) elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

### 3.5.1.FU] [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[700]. 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 [imipramine](#). 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 [imipramine](#) and perflutren[700] 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 QT interval prolongation
- 8) Literature Reports

a) Serious cardiopulmonary reactions, including fatalities, have been reported during or after administration of perflutren-containing microspheres; most serious reactions occurred within 30 minutes of administration. In 221 subjects receiving a perflutren-containing microsphere bolus injection of up to 10 microL/kg, measurement of ECG parameters from 1 hour to 72 hours after administration revealed QTc prolongations of greater than 30 milliseconds in 29% (64/221) of subjects. Among 46 subjects who were further evaluated, 39% experienced associated cardiac rhythm changes. The effects of concomitant drugs on ECG changes has not been studied [700].

### 3.5.1.FV] [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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.FW] [Phenelzine](#)

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

2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[584][585][586][587]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [588]. Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases [247]. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranlycypromine](#), and monitor patients closely [589][590].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [imipramine](#) with an monoamine oxidase inhibitor (MAOI) is contraindicated. If [imipramine](#) is replacing treatment with [phenelzine](#), a minimum of 2 weeks should elapse after [phenelzine](#) is discontinued before therapy with [imipramine](#) begins[247]. The manufacturer of [phenelzine](#) recommends that at least 10 days should elapse before [imipramine](#) therapy is replaced by [phenelzine](#) [565].

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers [247]. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [566][567][568][569][570][571]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [572].

b) Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar

reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [573].

c) A drug interaction was reported in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [574].

d) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [575].

e) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [576].

f) In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranlycypromine](#) in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to [disseminated intravascular coagulation](#) and eventual death [577].

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranlycypromine](#) in any combination, and d) close monitoring of patients [578] [568][569][579][580]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [581]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [581]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [582][569][583].

### 3.5.1.FX] Phenindione

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[711][712]. Considerable interindividual differences may be found [713].
- 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 dosage regimen which produces the desired level of [anticoagulation](#) may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.

**7)** Probable Mechanism: decreased phenindione metabolism; increased phenindione absorption

**8)** Literature Reports

**a)** In a study of healthy volunteers, the concurrent use of [nortriptyline](#) or [amitriptyline](#) resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects [708]. 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 [709]. 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 [710]. 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.FY] Phenmetrazine

**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](#) [510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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 [501][502][503][504]. 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 [501][502][503].



b)) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c)) 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 [506][504].

d)) 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](#) [507].

e)) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.FZ] [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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.GA| Phenprocoumon**

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[696][697]. Considerable interindividual differences may be found [698].
- 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 [693]. 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 [694]. 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 [695]. 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.GB| 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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that **methylphenidate** may inhibit the metabolism of some tricyclic antidepressants, such as **imipramine**, **clomipramine**, or **desipramine** [505].

c) 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 [506][504].

d) 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** [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.GC] **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[639]. The effects of **epinephrine** may be potentiated by tricyclic antidepressants [640] 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 [643][644][645][646].

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[639]. The effects of **epinephrine** may be potentiated by tricyclic antidepressants [640]. 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 [641].

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 [642].

### 3.5.1.GD] 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[598][599]. Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because phenytoin is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels.

3)) Severity: moderate

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: 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.GE] Pimozide

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

2)) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated[244]. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation [245][246].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.

7)) Probable Mechanism: additive effects on QT interval

8)) Literature Reports

a)) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day [243].

**3.5.1.GF] 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[769], such as [imipramine](#). 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 [imipramine](#), as this may result in additive effects on the QT interval and an increased risk of serious cardiovascular effects[769]. If concurrent therapy is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

**3.5.1.GG] 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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.GH] Procainamide**

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

2) Summary: Concomitant use of tricyclic antidepressants, including [imipramine](#), and class IA antiarrhythmics, including [procainamide](#), may increase the risk of [cardiotoxicity](#) due to similar cardiac effects of these drugs[282][283]. Therefore, monitoring the patient for signs and symptoms of [cardiac toxicity](#) during coadministration of [imipramine](#) and [procainamide](#) may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [imipramine](#) and [procainamide](#) may increase the risk of [cardiotoxicity](#) (increased PR interval, QRS complex, and QTc interval) due to similar cardiac effects of these drugs[282][283]. 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](#) [406].

### 3.5.1.GI] [Procarbazine](#)

1) Interaction Effect: [neurotoxicity](#), seizures

2) Summary: Concomitant tricyclic antidepressant and more potent MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. [Procarbazine](#) has relatively weak MAOI actions, so while the potential for drug interactions between tricyclic antidepressants and [procarbazine](#) exists, clinical data are lacking at this time[862][863]. Concurrent use is not recommended [864].

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use is not recommended and should probably be initiated only under close medical supervision, and then only if other antidepressant class agents have proven unsuccessful. With more potent MAOIs, recommendations for concurrent use of TCAs have included avoiding large doses of the TCA, using only oral tricyclics, and avoiding [imipramine](#), [clomipramine](#), and [desipramine](#). [Procarbazine](#) therapy should not begin until seven days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) [Procarbazine](#) is primarily used as an antineoplastic agent, but was originally investigated as a monoamine oxidase inhibitor [851]. Animal studies have indicated that [procarbazine](#) is a monoamine oxidase inhibitor (MAOI) [852] but appears to be a relatively weak MAOI in man [851]. Hypertensive reactions may still result from concomitant administration of tricyclic antidepressants, sympathomimetics, and tyramine containing foods [851][853].



b) Concomitant administration of monoamine oxidase (MAO) inhibitors with tricyclic antidepressants has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [854][855][856][857][858][859]. Careful examination of such reports indicate unusual circumstances in most cases such as [parenteral administration](#) of a tricyclic. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [860].

c) [Procarbazine](#) therapy should not begin until 7 days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors [861][851].

### 3.5.1.GJ] [Prochlorperazine](#)

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

2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines[435][436][437]. Other phenothiazines may have similar effects, though no reports are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation [438]. Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic antidepressants were taken together, likely due to inhibition of their metabolism [439][440][441][442].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent administration of a phenothiazine and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive effect on QT interval

### 3.5.1.GK] [Promethazine](#)

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

2) Summary: Both [imipramine](#) and [promethazine](#) may prolong the QT interval. Although this interaction has not been evaluated, the concomitant use of drugs that may prolong the QT interval, may increase the risk of QT interval prolongation and cardiac adverse events. If coadministration is required, monitoring for QT prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [imipramine](#) with other drugs that may prolong the QT interval, such as [promethazine](#), may increase the 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.GL] [Propafenone](#)

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

2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended[773][774][775].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [771].

b) A 68-year-old man suffering from agitated [major depression](#) was begun on a dose of [desipramine](#) 125 mg daily which produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An increased dose of 175 mg daily produced excellent clinical response with no side effects. He developed [atrial fibrillation and flutter](#). [Digoxin](#) 0.25 mg daily was added to his therapy, and [desipramine](#) was discontinued. His [arrhythmia](#) was suppressed with the addition of [propafenone](#) 150 mg twice daily and 300 mg at bedtime. [Desipramine](#) 150 mg daily was again begun, at which point he experienced dry mouth, sedation, and shakiness; the [desipramine](#) serum level was measured at 2092 nmol/L. The [desipramine](#) was discontinued for five days, the side effects ceased, and [desipramine](#) therapy was resumed at 75 mg daily. The [desipramine](#) serum level was measured at 1130 nmol/L [772].

### 3.5.1.GM] [Propranolol](#)

- 1) Interaction Effect: increased [imipramine](#) concentrations
- 2) Summary: One report of 2 cases of children receiving [imipramine](#) and [propranolol](#) was suggestive of interference with the metabolism of [imipramine](#) with this combination[648]. In one case, [imipramine](#) levels rose dramatically when the [propranolol](#) dose was increased following admission to the hospital. No toxicity was noted. The possibility that compliance prior to admission might have played a role was not considered by the authors, and no rechallenge was attempted. The other case involved several changes in dose of both drugs. Prospective study is needed to determine the validity of this interaction.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for an enhanced effect of [imipramine](#). A dosage adjustment may be required.
- 7) Probable Mechanism: decreased [imipramine](#) metabolism

### 3.5.1.GN] [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](#)[510][511]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [512]. 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 [513]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [514]. 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[501][502][503][504]. 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 [501][502][503].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [505].

c) 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 [506][504].

d) 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](#) [507].

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [508]. 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 [509].

### 3.5.1.GO] [Protriptyline](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [imipramine](#) and [protriptyline](#) is not common clinical practice. However if using concomitantly, use caution due to the potential for additive effects on QT interval prolongation[849]. If coadministration is required, caution should be used and monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [imipramine](#) and [protriptyline](#) is not common clinical practice. However if using concomitantly, use caution due to the potential for additive effects on QT interval prolongation[849]. 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.GP| Quetiapine

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

2J) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride[334], [haloperidol](#) [335], [risperidone](#) [336], sertindole [337], [quetiapine](#) [338], sultopride [339], and zotepine [340]. Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended [341][342].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7J) Probable Mechanism: additive cardiac effects

8J) Literature Reports

aJ) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [333].

### 3.5.1.GQ| Quinestrol

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

2J) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[475], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [476]. The effects of the interaction appear to be estrogen dose-related [477] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [478].

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: theoretical

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

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

8J) Literature Reports

aJ) 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 [466].

**b))** A case reported by [467] demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [468].

**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 [469].

**d))** The effect of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [470].

**e))** The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [471].

**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 [472].

**g)** Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [473]. 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 [474].

### 3.5.1.GR] [Quinidine](#)

**1)** Interaction Effect: increased [imipramine](#) plasma concentrations; an increased risk of [cardiotoxicity](#)

**2)** Summary: Concomitant use of [imipramine](#), a CYP2D6 substrate, and [quinidine](#), a CYP2D6 inhibitor, resulted in increased [imipramine](#) exposure[241]. 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 [287][288]. Monitoring the patient for increased [imipramine](#) side effects during concomitant use and for [imipramine](#) 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: probable

**6)** Clinical Management: Concomitant use of [imipramine](#) and [quinidine](#) may result in increased [imipramine](#) exposure[241]. 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 [282][283]. If [imipramine](#) and [quinidine](#) are coadministered, consider an [imipramine](#) dose adjustment. Conversely, if [quinidine](#) is discontinued from therapy, monitor for [imipramine](#) efficacy [241]. Also monitor the patient for signs and symptoms of [cardiac toxicity](#), including any changes in the ECG.

**7)** Probable Mechanism: inhibition of CYP2D6-mediated [imipramine](#) metabolism by [quinidine](#); additive [cardiac toxicity](#)

**8)** Literature Reports

**a)** Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of [imipramine](#) and [desipramine](#). Inhibition of this enzyme system can result in a 35% decrease in [imipramine](#) clearance and an 85% decrease in [desipramine](#) clearance. Demethylation of [imipramine](#) by the cytochrome P450 system is unaffected by this interaction. Until more information is available, all patients having [quinidine](#) added to a drug regimen containing [imipramine](#) or [desipramine](#) should be monitored for increased antidepressant serum concentrations and potential toxicity [284].

**b)** One study reported the cardiac effects of [imipramine](#) in 2 patients with depression and [cardiac arrhythmias](#) in a 7-week single-blind protocol of [imipramine](#) 3.5 mg/kg daily. The PR interval, QRS complex, and QTc interval all increased significantly in both cases, producing EKG changes similar to those of Type I antiarrhythmics ([quinidine](#), [procainamide](#), [disopyramide](#)). Each patient showed a decrease in both atrial and [ventricular premature depolarizations](#) during therapy. The first patient decreased from 33.4 atrial and 30.1 [ventricular premature depolarizations](#) per hour to 0.4 atrial and 0 [ventricular premature depolarizations](#) per hour. A second patient had 12.3 atrial and 169 [ventricular premature depolarizations](#) per hour prior to drug treatment which



decreased to 1.8 atrial and 28.1 [ventricular premature depolarizations](#) per hour during [imipramine](#) therapy. The investigators concluded that the doses of antiarrhythmic agents should be adjusted downward when used concurrently with tricyclic antidepressants due to an increased likelihood of [cardiotoxicity](#) [285].

c) In a placebo-controlled study, [imipramine](#) 3.5 mg/kg was administered daily to 7 patients with severe depression and doses were titrated 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 0 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](#) [286].

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

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Avoid using [quinine](#) concomitantly with other drugs that may cause QT prolongation, such as [imipramine](#), due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[699].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid using [quinine](#) concomitantly with other drugs that may cause QT prolongation, such as [imipramine](#), due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects[699].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.GT] [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 an antidepressant dose reduction may be needed[638].
- 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[638].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated tricyclic antidepressant metabolism

### 3.5.1.GU] [Rasagiline](#)

- 1) Interaction Effect: severe CNS toxicity

2) Summary: Concomitant use of [rasagiline](#) and tricyclic antidepressants should be avoided. Concurrent administration or overlapping therapy with tricyclic antidepressants and non-selective MAOIs has been reported to cause serious, sometimes fatal, reactions; the mechanisms of these reactions are not fully understood. Signs and symptoms include severe CNS toxicity (behavioral and mental status changes, diaphoresis, muscular rigidity, [hypertension](#), and syncope) associated with [hyperpyrexia](#) and death. Data from clinical studies, where rasagiline-treated patients (n=115) were concomitantly exposed to tricyclic antidepressants, are insufficient to rule out an interaction. At least 14 days should elapse after discontinuing [rasagiline](#) before initiating therapy with a tricyclic antidepressant[332].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [rasagiline](#) and a tricyclic antidepressant is not recommended. Wait at least 14 days after discontinuing [rasagiline](#) before initiating therapy with a tricyclic antidepressant[332].

7) Probable Mechanism: unknown

### 3.5.1.GV] [Risperidone](#)

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

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride[334], [haloperidol](#) [335], [risperidone](#) [336], sertindole [337], [quetiapine](#) [338], sultopride [339], and zotepine [340]. Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended [341][342].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [333].

### 3.5.1.GW] [Ritonavir](#)

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

2) Summary: Coadministered [ritonavir](#) may increase serum concentrations of [imipramine](#), resulting in [imipramine](#) toxicity[374]. Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with [ritonavir](#) [375].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs and symptoms of tricyclic antidepressant toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias). Reduce doses of imipramine as required.

7) Probable Mechanism: decreased imipramine metabolism

### 3.5.1.GX] Ropivacaine

1) Interaction Effect: increased plasma levels of ropivacaine

2) Summary: Ropivacaine is metabolized in the liver by the cytochrome P4501A enzyme system to 3-hydroxy ropivacaine, the major metabolite. Drugs which are metabolized by P4501A2 via competitive inhibition, such as imipramine, will potentially interact with the metabolism of ropivacaine. This would result in decreased renal clearance and increased plasma concentrations of ropivacaine[329].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Care must be taken to monitor the patient for signs of local anesthetic toxicity with the coadministration of ropivacaine and other drugs which are known to be metabolized by cytochrome P4501A2 via competitive inhibition, such as imipramine.

7) Probable Mechanism: inhibition of ropivacaine metabolism

### 3.5.1.GY] S-Adenosylmethionine

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

2) Summary: A single case has been reported of serotonin syndrome likely resulting from the combination of S-adenosylmethionine (S-AMe) and clomipramine[498]. S-AMe was shown to hasten the onset of therapeutic response of imipramine in a clinical trial involving 40 patients, without serotonergic side effects [499]. If therapy is initiated with S-AMe and a tricyclic antidepressant, the patient should be monitored closely for early signs of serotonin syndrome. Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result [500].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: S-adenosylmethionine (S-AMe) used concomitantly with imipramine was found to decrease depressive symptoms sooner than imipramine alone (Berlanger et al, 1992). One case has been reported of serotonin syndrome likely resulting from concomitant use of S-AMe and clomipramine (Iruela et al, 1993). If S-AMe and a tricyclic antidepressant are used together, use low doses of each and titrate upward slowly, while monitoring closely for early signs of serotonin syndrome such as increasing anxiety, confusion, and disorientation.

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

8) Literature Reports

a) A 71 year-old female was hospitalized with anxiety, agitation, confusion, and symptoms of serotonin syndrome. She had been taking S-adenosylmethionine 100 milligrams (mg) intramuscularly daily and clomipramine 25 mg daily for 10 days, which was then increased to 75 mg/day. Within 48-72 hours of the increased clomipramine dosage, she became progressively anxious, agitated, and confused. On admission she was verbally unresponsive and stuporous, with heart rate 130 beats/minute, respiratory rate 30 breaths/minute, temperature 40.5 degrees Celsius, diarrhea, myoclonus, generalized tremors, rigidity, hyperreflexia, shivering, diaphoresis,

and dehydration. Temperature increased to 43 degrees Celsius during her hospital stay, with no documented infection. White blood cell count (WBC) was 13,040 mm<sup>3</sup>, lactic dehydrogenase was 662 units/liter (U/L), creatine phosphokinase was 8920 U/L, serum potassium 2.7 milliequivalents/liter (mEq/L), [creatinine](#) 1.1 mg/100 milliliter (mL) (laboratory reference values were not provided). A cranial [computed tomography](#) (CT) scan was normal. The patient was not taking neuroleptics. Serum benzodiazepine and tricyclic antidepressant levels were normal. Symptoms resolved gradually with 4 days of hydration and supportive care. The interaction was proposed to be a result of synergistic activity of S-adenosylmethionine and [clomipramine](#) [497].

### 3.5.1.GZ| 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[278]. 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.HA| Saquinavir

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: The concomitant use of ritonavir-boosted [saquinavir](#) with other drugs that may cause QT interval prolongation, such as [imipramine](#), 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 [imipramine](#) or ritonavir-boosted [saquinavir](#) or both[345]. Additionally, monitoring of [imipramine](#) concentrations is recommended during coadministration as [amitriptyline](#) levels may increase [241].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ritonavir-boosted [saquinavir](#) with other drugs that may cause QT interval prolongation, such as [imipramine](#), 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 [imipramine](#) or ritonavir-boosted [saquinavir](#) or both[345]. Additionally, monitoring of [imipramine](#) concentrations is recommended during coadministration as [amitriptyline](#) levels may increase [241].

7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.HB| [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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.HC| [Selegiline](#)

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

2) Summary: Coadministration of [imipramine](#) and [selegiline](#) is contraindicated[247][366]. Concomitant tricyclic antidepressants (TCAs) and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#) [367][368][369][370]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), [myoclonus](#), and changes in mental status [371]. A minimum of 14 days should elapse after discontinuing [selegiline](#) before initiating therapy with [imipramine](#). A time period of 4 to 5 half-lives, approximately 1 week, should elapse after discontinuing [imipramine](#) prior to initiating therapy with [selegiline](#) [366].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of [imipramine](#) with [selegiline](#) is contraindicated. A minimum of 14 days should elapse after discontinuing [selegiline](#) before initiating therapy with [imipramine](#). A time

period of 4 to 5 half-lives, approximately 1 week, should elapse after discontinuing [imipramine](#) prior to initiating therapy with [selegiline](#).

7) Probable Mechanism: altered catecholamine uptake and metabolism

#### 8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [247][347][348][349][350][351][352]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [353].

b) Coadministration of [selegiline](#) with TCAs such as [protriptyline](#) or [amitriptyline](#) has resulted in severe CNS toxicity, [hyperpyrexia](#) and death. Combination of [selegiline](#) with various other tricyclic antidepressants has caused numerous side effects, including [hypertension](#), syncope, and muscular rigidity [354].

c) Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [355].

d) A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [356].

e) A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [357].

f) Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [358].

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



symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to [disseminated intravascular coagulation](#) and eventual death [359].

**h)** There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#), [desipramine](#), and [tranylcypromine](#) in any combination, and d) close monitoring of patients [360] [349][350][361][362]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [363]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [363]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [364][350][365].

### 3.5.1.HD] Sematilide

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

**2)** Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[424], [amiodarone](#) [425], azimilide [426], [bretylium](#) [427], [ibutilide](#) [428], sematilide [429], [dofetilide](#) [430], and [sotalol](#) [431]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [432][433].

**3)** Severity: major

**4)** Onset: rapid

**5)** Substantiation: theoretical

**6)** Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

**7)** Probable Mechanism: additive QT prolongation

**8)** Literature Reports

**a)** EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [422].

**b)** Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetry monitoring is advised [423].

### 3.5.1.HE] Sertindole

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

**2)** Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride[334], [haloperidol](#) [335], [risperidone](#) [336], sertindole [337], [quetiapine](#) [338], sultopride [339], and zotepine [340]. Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended [341][342].

**3)** Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [333].

### 3.5.1.HF] [Sertraline](#)

- 1) Interaction Effect: modest elevations in [imipramine](#) serum levels or possible [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: There is limited evidence suggesting that [sertraline](#) may inhibit tricyclic antidepressant (TCA) metabolism resulting in higher TCA serum concentrations. Sertraline inhibits cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic antidepressants[594][595][596]. Effects of the interaction may have little or no clinical impact, however. Increases in TCA serum levels associated with [sertraline](#) coadministration were modest compared with those found when [fluoxetine](#) (another selective serotonin reuptake inhibitor) was combined with [desipramine](#) [597]. Monitor patients on imipramine-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). [Imipramine](#) doses may need to be reduced.
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may result in the inhibition of the TCA metabolism. A few cases of [serotonin syndrome](#) have also been reported with concurrent TCA and SSRI therapy. Caution should be observed when drugs in these two classes are used together.
- 7) Probable Mechanism: inhibition of [imipramine](#) metabolism
- 8) Literature Reports

a) [Desipramine](#) pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received only [desipramine](#) (50 mg daily) for 7 days followed by [desipramine](#) with [sertraline](#) (50 mg daily) for 21 days. When [sertraline](#) was added to [desipramine](#) therapy, the mean maximum concentration of [desipramine](#) increased by 34% and the area under the concentration-time curve increased by 26%. Trough concentrations of [desipramine](#) were close to baseline one week after [sertraline](#) was discontinued. The changes in [desipramine](#) concentrations were modest and the interaction may not be clinically significant [593].

### 3.5.1.HG] [Sodium Phosphate](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Sodium phosphate](#) has been associated with prolongation of the QT interval. Use caution when using [imipramine](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on QT

interval prolongation and an increased risk of serious cardiovascular effects[387]. 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 [imipramine](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects[387]. If concurrent therapy is required, monitor closely for QT prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

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

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

2) Summary: [Sodium phosphate](#) has been associated with prolongation of the QT interval. Use caution when using [imipramine](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects[387]. 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 [imipramine](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects[387]. If concurrent therapy is required, monitor closely for QT prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

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

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

2) Summary: [Sodium phosphate](#) has been associated with prolongation of the QT interval. Use caution when using [imipramine](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects[387]. 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 [imipramine](#) and [sodium phosphate](#) concomitantly due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects[387]. If concurrent therapy is required, monitor closely for QT prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

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

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

2) Summary: 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 should be approached with caution as coadministration may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#)[705]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the concomitant use of [solifenacin](#) with other drugs that may prolong the QT interval, such as [imipramine](#), as coadministration may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#)[705]. 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.HK] [Sorafenib](#)

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

2) Summary: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), caution is advised when using [sorafenib](#) with other drugs that may increase the QT interval, such as [imipramine](#). If coadministration is required, [monitoring of ECG](#) and electrolytes ([calcium](#), [magnesium](#), and [potassium](#)) is recommended[390].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), caution is advised when using [sorafenib](#) with other drugs that may increase the QT interval, such as [imipramine](#). If coadministration is required, [monitoring of ECG](#) and electrolytes ([calcium](#), [magnesium](#), and [potassium](#)) is recommended[390].

7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.HL] [Sotalol](#)

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

2) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including [acecainide](#)[424], [amiodarone](#) [425], [azimilide](#) [426], [bretylum](#) [427], [ibutilide](#) [428], [sematilide](#) [429], [dofetilide](#) [430], and [sotalol](#) [431]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [432][433].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [422].

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised [423].

### 3.5.1.HM] [Sparfloxacin](#)

1) Interaction Effect: prolongation of the QTc interval and/or [torsades de pointes](#)

2)) Summary: **Torsades de pointes** has been reported in patients receiving **sparfloxacin** concomitantly with **disopyramide** and **amiodarone**. The use of **sparfloxacin** is contraindicated with drugs which produce an increase in the QTc interval and/or **torsades de pointes**, including tricyclic antidepressants. **Sparfloxacin** is also contraindicated in persons with known QTc prolongation[722].

3)) Severity: contraindicated

4)) Onset: delayed

5)) Substantiation: theoretical

6)) Clinical Management: **Sparfloxacin** is contraindicated in individuals with known QTc prolongation or in patients being treated concurrently with drugs that are known to increase the QTc interval and/or cause **torsades de pointes**.

7)) Probable Mechanism: additive effects on QTc prolongation

8)) Literature Reports

a)) In clinical trials involving 1489 patients with a baseline QTc measurement, the mean prolongation of the QTc interval at **sparfloxacin** steady-state was 10 msec (2.5%). Of these subjects, 0.7% had a QTc interval greater than 500 msec at steady-state. However, no arrhythmic effects were seen in any of the patients. The magnitude of the QTc effect does not increase with repeated administration of **sparfloxacin**, and the QTc interval returns to baseline within 48 hours after discontinuation of **sparfloxacin** [720].

b)) A case of **sparfloxacin**-induced **torsades de pointes** is described [721]. A 47-year old woman hospitalized for suppurative **otitis media** and **mastoiditis** was treated with **sparfloxacin** due to an allergy to betalactam antibiotics. On day six of treatment she felt dizzy and lost consciousness. This was attributed to **torsades de pointes** on the **cardioscope** and was followed by **cardiac arrest** which required **cardiopulmonary resuscitation**. Her pre-treatment **electrocardiogram** showed QT and QTc intervals of 0.34 and 0.46 seconds, respectively. An **electrocardiogram** post-arrest revealed QT and QTc intervals of 0.35 and 0.60 seconds, respectively. A 24-hour continuous **electrocardiography** confirmed numerous episodes of **torsades de pointes** occurring after episodes of sino-auricular block. **Sparfloxacin** was discontinued and the QTc returned to baseline within a week. Upon further testing, it was determined that the patient suffered from a mild idiopathic **long QT syndrome**. Due to the onset of symptoms with administration of **sparfloxacin** and the relief of symptoms following discontinuation of the drug, it is highly probable that **sparfloxacin** contributed to the **torsades de pointes**.

### 3.5.1.HN] Spiramycin

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

2)) Summary: Tricyclic antidepressants (TCAs) and spiramycin have been shown to prolong the QTc interval at the recommended therapeutic dose[684][685]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as spiramycin, is not recommended [686].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concurrent administration of spiramycin and tricyclic antidepressants is not recommended.

7)) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.HO] 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[411][412], [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 [413], as well as concomitant use of monoamine oxidase inhibitors with tricyclic antidepressants [414][415][416]. Coadministration of [amitriptyline](#) and St. John's Wort decreased the area under the concentration-time curve of [amitriptyline](#) and its metabolite [nortriptyline](#) [417]; 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.HP] [Sulfamethoxazole](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) and cotrimoxazole have been shown to prolong the QTc interval at the recommended therapeutic dose[494][495]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as cotrimoxazole, is not recommended [496].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

#### 3.5.1.HQ] [Sultopride](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride[334], [haloperidol](#) [335], [risperidone](#) [336], sertindole [337], [quetiapine](#) [338], sultopride [339], and zotepine [340]. Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended [341][342].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports



a)) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [333].

### 3.5.1.HR] [Sunitinib](#)

- 1)) Interaction Effect: an increased risk of QT interval prolongation
- 2)) Summary: Use caution when using [imipramine](#) and [sunitinib](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels[394].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution when using [imipramine](#) and [sunitinib](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels[394].
- 7)) Probable Mechanism: additive effects on the QT interval

### 3.5.1.HS] [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[405].
- 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[405].
- 7)) Probable Mechanism: additive serotonergic effect

### 3.5.1.HT] [Tedisamil](#)

- 1)) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), cardiac arrest)
- 2)) Summary: Cases of QTc prolongation and/or [torsades de pointes](#) have been reported with all Class III antiarrhythmic agents, including acecainide[424], [amiodarone](#) [425], azimilide [426], [bretylum](#) [427], [ibutilide](#) [428], sematilide [429], [dofetilide](#) [430], and [sotalol](#) [431]. Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended [432][433].
- 3)) Severity: major

- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, [intraventricular conduction delays](#), increased corrected QT interval (QTc) and flattened T waves [422].

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. [Dofetilide](#) should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised [423].

### 3.5.1.HU] 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[725], such as [imipramine](#). 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[725], such as [imipramine](#). 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 [725].

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 [725].

### 3.5.1.HV] Telithromycin

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Telithromycin](#) may prolong the QT interval in some patients[409]. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [telithromycin](#) and tricyclic antidepressants is not recommended [410].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of [telithromycin](#) and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.HW] Terfenadine

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose[748]. Even though no formal drug interaction studies have been done, the coadministration of [terfenadine](#) and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is contraindicated [749][750].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [terfenadine](#) with any drug that prolongs the QT interval, such as tricyclic antidepressants, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.HX] Teriflunomide

- 1) Interaction Effect: reduced [imipramine](#) exposure
- 2) Summary: During a study of repeated doses of teriflunomide administered concomitantly with [caffeine](#), a CYP1A2 substrate, mean C<sub>max</sub> and AUC of [caffeine](#) were reduced 18% and 55%, respectively, suggesting that teriflunomide is a weak CYP1A2 inducer[757]. Therefore the coadministration of CYP1A2 substrates, such as [imipramine](#), and teriflunomide may result in reduced [imipramine](#) exposure due to induction of CYP1A2 by teriflunomide. Monitor patients for decreased efficacy of [imipramine](#) if used concomitantly with teriflunomide.[757].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [imipramine](#), a CYP1A2 substrate, and teriflunomide, a weak CYP1A2 inducer, may reduce exposure to [imipramine](#). Monitor patients for decreased efficacy of [imipramine](#) if used concomitantly with teriflunomide[757].
- 7) Probable Mechanism: induction of CYP1A2-mediated [imipramine](#) metabolism by teriflunomide

**3.5.1.HY] Tetrabenazine**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: The concomitant use of tetrabenazine with other drugs that may cause QT interval prolongation, such as [imipramine](#), should be avoided due to an increased risk of serious cardiac adverse events, including [torsade de pointes](#)[396]. If concurrent therapy is required, consider monitoring for QT prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of tetrabenazine with other drugs that may cause QT interval prolongation, such as [imipramine](#), should be avoided due to an increased risk of serious cardiac adverse events, including [torsade de pointes](#)[396]. If concurrent therapy is required, consider monitoring for QT prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

**3.5.1.HZ] 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[561][562][563]. In addition, TCAs can worsen seizure control by reducing the seizure threshold [564]. 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 [560]. 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.IA] Thioridazine**

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

- 2) Summary: Although citing no data, the manufacturer of [thioridazine](#) states that concomitant use with other drugs which prolong the QT interval is contraindicated[681]. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation [682].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of a tricyclic antidepressant and [thioridazine](#) is contraindicated.
- 7) Probable Mechanism: additive effect on QT interval

### 3.5.1.IB] Tibolone

- 1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, [akathisia](#))
- 2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[490], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [491]. The effects of the interaction appear to be estrogen dose-related [492] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on [estrogen therapy](#) [493].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
- 7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
- 8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received [imipramine](#) (150 milligrams/day) and placebo, 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (50 micrograms/day), while 5 patients received [imipramine](#) (150 milligrams/day) and [ethinyl estradiol](#) (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and [imipramine](#) demonstrated a significantly greater improvement in symptoms than did the 10 patients taking [imipramine](#) alone. However, after 2 weeks, the 5 patients that received [imipramine](#) and high-dose estrogen had not improved as much as the patients receiving [imipramine](#) and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking [imipramine](#). Following the discontinuation of [ethinyl estradiol](#), a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received [imipramine](#) 150 milligrams and [ethinyl estradiol](#) 50 micrograms daily did not improve as much as 10 patients receiving only [imipramine](#). Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [481].

b) A case reported by [482] demonstrated an interaction in a 32-year-old female taking [conjugated estrogens](#) 2.5 milligrams and [imipramine](#) 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches,

and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [483].

c) In a study women received [clomipramine](#) and oral contraceptives or [clomipramine](#) alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking [clomipramine](#) alone. No significant difference was noted in the patients' responses to [clomipramine](#). It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [484].

d) The effect of oral contraceptives on [clomipramine](#) was studied in 42 women between the ages of 18 and 40. Twenty-three women took [clomipramine](#) 25 milligrams at bedtime while 19 took [clomipramine](#) 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum [clomipramine](#) concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of [clomipramine](#) given [485].

e) The onset of [akathisia](#) was reported in 3 patients receiving [conjugated estrogens](#) and tricyclic antidepressants concurrently. A 24-year-old patient receiving [clomipramine](#) 120 milligrams/day for [anorexia nervosa](#) and [conjugated estrogens](#) 1.25 milligrams/day for [amenorrhea](#) developed [restless legs](#) and a constant desire to move continuously. Estrogen was discontinued and [benztropine](#) 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. LI [Akathisia](#) and disorientation developed in a 55-year-old patient on [conjugated estrogens](#) 1.25 milligrams/day who was prescribed [amitriptyline](#) 50 milligrams/day for depression. Within hours of [amitriptyline](#), the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing [amitriptyline](#). Positive rechallenge at one week with [doxepin](#) 100 milligrams, with resolution following discontinuation of [doxepin](#). A third case of [akathisia](#) was reported in a 35-year-old patient who received [conjugated estrogens](#) 1.25 milligrams/day and [amitriptyline](#) 50 milligrams/day. [Akathisia](#) developed within a few hours after taking the first dose of [amitriptyline](#) and resolved within 48 hours following discontinuation of the antidepressant [486].

f) The absolute bioavailability of [imipramine](#) increased in women who received low-dose oral contraceptives (50 micrograms or less of [ethinyl estradiol](#)) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [487].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [488]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [489].

### 3.5.1.IC] Toloxatone

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

2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin](#)



[syndrome](#)[948][949][950][951]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), myoclonus, and changes in mental status [952]. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranylcypromine](#), and monitor patients closely [953][954].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

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

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [938][939][940][941]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [942].

b) There is minimal risk of a clinically significant pharmacokinetic interaction between [amitriptyline](#) and toloxatone, a MAOI-A [943]. Seventeen inpatients being treated for major depressive illness were administered [amitriptyline](#) 125 mg once daily for two weeks, and the following two weeks they received [amitriptyline](#) 125 mg daily and toloxatone 600 mg daily. With combined therapy there was a small, nonsignificant increase in [amitriptyline](#) plasma levels. The availability and urinary excretion of [amitriptyline](#) and its metabolites were not significantly affected.

c) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [944]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added [892]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [945][940][946].

d) [Serotonin syndrome](#) has been reported with the use of moclobemide, a reversible inhibitor of monoamine oxidase, and a TCA. A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [947].

### 3.5.1.ID] [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 [imipramine](#), should be avoided. If treatment with [imipramine](#) is warranted, interrupt [toremifene](#) therapy; however, if coadministration of [imipramine](#) 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[726].

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 [imipramine](#), may result in additive effects on the QT interval and should be avoided. If treatment with [imipramine](#) 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[726].

7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.IE] [Tramadol](#)

1) Interaction Effect: an increased risk of seizures

2) Summary: Seizures have been reported in patients using [tramadol](#). Some medications, including tricyclic antidepressants (TCAs), are known to reduce the seizure threshold. The risk of seizures may be enhanced when [imipramine](#) and [tramadol](#) therapy are combined[689].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution should be used if [tramadol](#) is to be administered to patients receiving concomitant TCA therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.

7) Probable Mechanism: unknown

### 3.5.1.IF] [Tranlycypromine](#)

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

2) Summary: Concomitant TCA and MAOI use has resulted in [hyperpyrexia](#), convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed [serotonin syndrome](#)[623][624][625][626]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by [hypertension](#), [hyperthermia](#), [myoclonus](#), and changes in mental status [627]. Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid [imipramine](#), [clomipramine](#), [desipramine](#), and [tranlycypromine](#), and monitor patients closely [628][629].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [imipramine](#) with a monoamine oxidase inhibitor (MAOI), such as [tranlycypromine](#) is contraindicated. If [imipramine](#) is replacing treatment with [tranlycypromine](#), a minimum of 14 days should elapse after [tranlycypromine](#) is discontinued before therapy with [imipramine](#) begins[247]. The manufacturer of [tranlycypromine](#) recommends that at least 7 days should elapse before [tranlycypromine](#) therapy is replaced by [imipramine](#). Similarly, if [imipramine](#) therapy is substituted by [tranlycypromine](#), there should be a 7 day washout period. [Tranlycypromine](#) should then be given using half the normal starting dosage for, minimally, the first week of therapy [604].

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

**a)** Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers [247]. Reports of excitation, [hyperpyrexia](#), convulsions, and possible death have been attributed to the combination [605][606][607][608][609][610]. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism [611].

**b)** Administration of a TCA after MAOI therapy may result in the development of [serotonin syndrome](#). In a double-blind, crossover study examining the effects of clorgyline and [clomipramine](#) for the treatment of [obsessive-compulsive disorder](#), two subjects developed severe reactions characteristic of [serotonin syndrome](#). During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent [clomipramine](#) therapy. After taking the first 100 mg dose of [clomipramine](#), one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and [arrhythmia](#). Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with [clomipramine](#) without adverse effects [612].

**c)** A drug interaction occurred in a 76-year old woman who had been taking [clomipramine](#) 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further [mental impairment](#), muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for [serotonin syndrome](#) and were resolved a few days later after discontinuing all antidepressant medications [613].

**d)** A 39-year old woman with [bipolar disorder](#) developed [serotonin syndrome](#) after [imipramine](#) was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when [imipramine](#) was started at 50 mg daily, followed by two dosage increases of [imipramine](#) to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in [imipramine](#) to 200 mg per day, the patient developed symptoms of [serotonin syndrome](#), including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with [chlorpromazine](#) and symptoms resolved over the next few days without further complications [614].

**e)** Three patients with [bipolar disorder](#) developed manic symptoms while undergoing concurrent therapy with [isocarboxazid](#) and [amitriptyline](#). In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect [615].

**f)** In one case, [clomipramine](#) 10 mg twice daily was added to a stable regimen of [tranylcypromine](#) in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to [disseminated intravascular coagulation](#) and eventual death [616].

**g)** There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg [amitriptyline](#) or its equivalent, 45 mg [phenelzine](#), or 60 mg [isocarboxazid](#)) b) oral administration c) avoidance of [clomipramine](#), [imipramine](#),

desipramine, and [tranylcypromine](#) in any combination, and d) close monitoring of patients [617][607][608][618][619]. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started [620]. Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of [amitriptyline](#) and [isocarboxazid](#) is preferred [620]. Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs [621][608][622].

### 3.5.1.IG| [Trazodone](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation and [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#). Both [imipramine](#) and [trazodone](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive effects and the potential for increased risk of [serotonin syndrome](#)[543]. 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 [378]. If coadministration of [imipramine](#) and [trazodone](#) is required, monitoring for QT interval prolongation and signs and symptoms of [serotonin syndrome](#) may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [imipramine](#), may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#). Coadministration may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[543]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation; additive serotonergic effects

### 3.5.1.IH| [Trifluoperazine](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines[435][436][437]. Other phenothiazines may have similar effects, though no reports are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation [438]. Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic antidepressants were taken together, likely due to inhibition of their metabolism [439][440][441][442].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent administration of a phenothiazine and a tricyclic antidepressant is not recommended.
- 7) Probable Mechanism: additive effect on QT interval

**3.5.1.II] Trimethoprim**

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Tricyclic antidepressants (TCAs) and cotrimoxazole have been shown to prolong the QTc interval at the recommended therapeutic dose[494][495]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as cotrimoxazole, is not recommended [496].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

**3.5.1.IJ] Tryptophan**

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2) Summary: [Imipramine](#) decreases reuptake of serotonin, potentially increasing the risk of [serotonin syndrome](#) when [imipramine](#) is used concomitantly with other serotonergic agents[958]. Tryptophan increases serotonin levels and may produce additive serotonergic effects when taken concurrently with [imipramine](#). Use caution if [imipramine](#) and tryptophan are coadministered and consider monitoring 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 [imipramine](#) and tryptophan 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.IK] Vandetanib**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: The concomitant use of vandetanib with other drugs that may cause QT interval prolongation, such as [imipramine](#), should be avoided due to an increased risk of serious cardiac adverse events, including [torsade de pointes](#). If concurrent therapy is required, more frequent [ECG monitoring](#) is recommended[376].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of vandetanib with other drugs that may cause QT interval prolongation, such as [imipramine](#), should be avoided due to an increased risk of serious cardiac adverse events, including [torsade de pointes](#). If concurrent therapy is required, more frequent [ECG monitoring](#) is recommended[376].
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.IL] Vardenafil**

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Both [imipramine](#) and [varденаfil](#) have been associated with QT interval prolongation[479][480]. Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), caution is advised when using [varденаfil](#) concomitantly with drugs that prolong the QT interval, such as [imipramine](#) [480]. 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 [imipramine](#) and [varденаfil](#) may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), and therefore caution is advised[479][480]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.IM] [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[670][671][672][673][674][675][676][677][678][679]. 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.IN] [Vemurafenib](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Vemurafenib is a weak CYP2D6 inhibitor and may cause QT interval prolongation. Concomitant use of vemurafenib and a CYP2D6 substrate, such as [imipramine](#)[241], can lead to elevated drug levels of the CYP2D6 substrate. As some CYP2D6 substrates can also prolong the QT interval, there is potential for additive QT prolongation. Therefore, vemurafenib should not be coadministered with CYP2D6 substrates that possess cardiac effects [382]. If concomitant use is required, consider a dose reduction for [imipramine](#) and monitoring of [imipramine](#) concentrations [382][241].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Vemurafenib is a weak CYP2D6 inhibitor and may cause QT interval prolongation. Concomitant use of vemurafenib and a CYP2D6 substrate, such as [imipramine](#)[241], can lead to elevated drug levels of the CYP2D6 substrate. As some CYP2D6 substrates can also prolong the QT interval, there is potential for additive QT prolongation. Therefore, vemurafenib should not be coadministered with CYP2D6 substrates that possess cardiac effects [382]. If concomitant use is required, consider a dose reduction for [imipramine](#) and monitoring of [imipramine](#) concentrations [382][241].
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.IO] [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[631][632]. 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 [633]. In addition, [venlafaxine](#) and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [634][631][635]. [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 [630].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of [venlafaxine](#) and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: decreased TCA and [venlafaxine](#) metabolism; additive effects on QT prolongation
- 8) Literature Reports

a) When administered with [imipramine](#), the pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected. [Venlafaxine](#) increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of [desipramine](#) by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold ([venlafaxine](#) 37.5 mg every 12 hours) and by 4.5-fold ([venlafaxine](#) 75 mg every 12 hours). The clinical significance of this finding is unknown [630].

### 3.5.1.IP] [Verapamil](#)

- 1) Interaction Effect: [imipramine](#) toxicity (dry mouth, sedation, urinary retention)
- 2) Summary: [Verapamil](#) decreased [imipramine](#) clearance by 25% (statistically significant) compared with placebo in a controlled, single-dose study in 12 healthy volunteers[850]. [Imipramine](#) bioavailability was slightly increased by [verapamil](#) (15% greater than with placebo). The clinical significance of this interaction and whether it occurs with other tricyclic antidepressants has yet to be determined.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for anticholinergic side effects of [imipramine](#) if [verapamil](#) is added to therapy; lower doses of [imipramine](#) may be appropriate. Conversely, if [verapamil](#) is discontinued, monitor continued clinical efficacy of [imipramine](#) and adjust dosage accordingly.
- 7) Probable Mechanism: decreased [imipramine](#) clearance

### 3.5.1.IQ] [Voriconazole](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Caution is advised with the concomitant use of [voriconazole](#) and other QT prolonging drugs, such as [imipramine](#), as this may result in additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsades de pointes](#) and/or sudden death[384]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: Caution is advised with the concomitant use of [voriconazole](#) and other QT prolonging drugs, such as [imipramine](#), as this may result in additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsades de pointes](#) and/or sudden death[384]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.IR| [Warfarin](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants[450][451]. Considerable interindividual differences may be found [452].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: In patients receiving [imipramine](#) and [warfarin](#), closely monitor prothrombin time ratio and adjust [warfarin](#) doses accordingly.
- 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 [447]. This effect was not observed with [warfarin](#).

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

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

### 3.5.1.IS| [Ziprasidone](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Ziprasidone](#) use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided[330][331].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of [ziprasidone](#) and agents that can prolong the QTc interval[330].
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.IT| [Zolmitriptan](#)

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

2) Summary: Tricyclic antidepressants (TCAs) and [zolmitriptan](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[651][652]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [zolmitriptan](#), is not recommended [653].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of [zolmitriptan](#) and tricyclic antidepressants is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.IU] Zotepine

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

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride[334], [haloperidol](#) [335], [risperidone](#) [336], sertindole [337], [quetiapine](#) [338], sultopride [339], and zotepine [340]. Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended [341][342].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with [pimozide](#) have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving [pimozide](#) doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmias](#) [333].

### 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[979][980][981][982][983]. There are no studies evaluating respiratory response with the combination.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Encourage abstinence from alcohol during at least the first few weeks of tricyclic administration to allow patient accommodation to potential CNS depressant effects of the tricyclic.

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 [974].

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](#) [975].

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 [976].

d)) Individual case reports have documented "blackouts" following modest amounts of alcohol in combination with either [amitriptyline](#) or [imipramine](#) [977], and reversible extrapyramidal effects (parkinsonian effects, [akathisia](#)) with [amoxapine](#) [978].

### 3.5.4] Drug-Tobacco Combinations

#### 3.5.4.A] Tobacco

- 1)) Interaction Effect: decreased [imipramine](#) concentrations
- 2)) Summary: The administration of oral [imipramine](#) 3.5 mg/kg to tobacco smokers (15 cigarettes daily) resulted in significantly lower mean plasma levels of combined [imipramine](#) and desmethyylimipramine (160 ng/mL) when compared to nonsmokers (290 ng/mL)[984]. Tobacco smoking may alter the response to antidepressants [985][984].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Patients who smoke may require larger doses of [imipramine](#) than non-smokers. Monitor smokers receiving [imipramine](#) for antidepressant efficacy.
- 7)) Probable Mechanism: increased hepatic metabolism

### 3.5.5] Intravenous Admixtures

#### 3.5.5.1] Drugs

##### 3.5.5.1.A] [Doxapram](#)

##### 1)) Compatible

a)) [Doxapram](#) (400 mg/20 mL with [imipramine](#) 12.5 mg/1 mL physically compatible and no loss of [doxapram](#) reported; [imipramine](#) stability not described) [1526]

b)) [Imipramine](#) (12.5 mg/1 mL with [doxapram](#) 400 mg/20 mL physically compatible in syringe with no [doxapram](#) decomposition in 24 hours; temperature not specified) [1527]

##### 3.5.5.1.B] [Haloperidol](#)

##### 1)) Conflicting Data

a)) Incompatible

1) **Haloperidol** in a 1:1 or 1:2 mixture with **imipramine**, compatibility is questionable because the mixture exhibited no visual changes in 1 hour, was slightly cloudy and viscous in 2 hours, was clear and very viscous in 4 hours at room temperature, but no **haloperidol** decomposition was observed in a 4 hour study period; drug concentrations not specified [1528]

**b) Compatible**

1) **Haloperidol** in a 1:1 or 1:2 mixture with **imipramine**, compatibility is questionable because the mixture exhibited no visual changes in 1 hour, was slightly cloudy and viscous in 2 hours, was clear and very viscous in 4 hours at room temperature, but no **haloperidol** decomposition was observed in a 4 hour study period; drug concentrations not specified [1529]

## 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) **Imipramine** Hydrochloride

##### 1) Therapeutic

##### a) Laboratory Parameters

##### 1) MHPG Urinary Concentration

a) Patients with urinary levels of 3-methoxy-4-hydroxy-phenyl glycol (MHPG) less than 1950 mcg/day, prior to tricyclic antidepressant (TCA) therapy, respond to imipramine, and other TCAs, more predictably than patients with MHPG urinary levels greater than 1950 mcg/day [1045]; (Beckmann & Goodwin, 1975)[1046].

b) Newer data [1047] confirm some of the earlier data and hypotheses while failing to confirm others. The fact that a low cerebrospinal fluid (CSF) 5-HIAA (5-hydroxyindoleacetic acid) or low urinary MHPG value during the pretreatment period is associated with a favorable response to amitriptyline therapy was not confirmed. In fact, the study showed no significant relationships between pretreatment urinary MHPG, CSF MHPG, 5-HIAA, or HVA (homovanillic acid) values and subsequent amitriptyline efficacy.

c) Low urinary NE and MHPG values are associated with a greater incidence of response to amitriptyline or imipramine therapy in bipolar affective disorder patients, but not in unipolar patients [1048].

## **2j) Dexamethasone Suppression Test (DST)**

**a)** The DST has been reported to be a useful tool in predicting whether or not a patient would respond to tricyclic antidepressant therapy (Brown et al, 1979, Brown et al, 1980). Eighty percent of patients with a positive DST responded to therapy versus a 37% response rate in patients with a negative DST [1049]. The usefulness of DST results as an indicator of tricyclic antidepressant therapy efficacy in the treatment of depression were not confirmed in one study [1050].

**b)** Depressed patients with abnormal DST may respond better to imipramine or desipramine therapy than amitriptyline or clomipramine therapy [1051]. The result of this study must be considered with caution since the investigator made a single evaluation of efficacy after 2 weeks of therapy. These results were not replicated utilizing imipramine and amitriptyline therapy [1052]. Therefore, DST results may not be a useful tool in the selection of a particular antidepressant.

## **3j) Platelet Monoamine Oxidase Activity**

**a)** Measurements of platelet MAO activity with serotonin reveals that unmedicated depressed patients have a significantly higher degree of activity compared to controls. This degree of activity decreases progressively during imipramine therapy and falls within normal limits at the time the patient is classified as recovered [1053]. Whether platelet MAO activity is useful as a monitoring parameter remains to be determined.

## **4j) Platelet Binding**

**a)** Imipramine has been shown to have specific high-affinity binding sites on human platelet membranes [1054]. These binding sites appear to be similar to those found in the human brain. Recent evidence indicates that platelet membrane binding may be decreased in some depressed patients [1054][1055][1056]; (Ambrusini et al, 1992). The exact value of this finding is still unknown; however, it may be of value in predicting which depressed patients are more likely to respond to antidepressant therapy.

**b)** The ability of the platelet to bind imipramine decreases with age. Whether this decrease in platelet binding is related to decreases in the density or number of receptors or an alteration in membrane microenvironment is unknown. Even though the decrease in platelet binding is significant, whether the changes effects the efficacy of the drug is unknown [1057].

**c)** Significant reductions in platelet imipramine binding have been observed in depressed patients. However, patients diagnosed with panic disorders or panic disorders concurrent with depression and patients with a previous history of depression have normal platelet imipramine binding compared to controls. The reason for this difference is unknown, but may indicate that the 2 syndromes differ neurochemically [1055].

## **5j) Serum Concentrations**



**a) Indications for determination of serum imipramine concentration [1058]:**

- 1) Utilization of adequate doses without experience clinical effect;**
- 2) Side effects uncertainly related to imipramine therapy;**
- 3) Monitoring high dose imipramine therapy;**
- 4) Assess the influence of intercurrent illness on imipramine serum concentrations;**
- 5) Evaluating a patient suspected of intentional or unintentional overdose of imipramine.**

**b) Physical Findings**

**1) Depression**

- a) Clinical improvement of the signs and symptoms of depression.**

**2) Enuresis**

- a) Decreased frequency of nocturnal wetting episodes.**

**3) Attention Deficit Hyperactivity Disorder (ADHD)**

- a) Improvement in mental and behavioral symptoms, including inappropriate inattention, impulsivity, hyperactivity, and cognitive performance.**

**2) Toxic**

**a) Laboratory Parameters**

- 1) Obtain WBC and differential cells in patients with fever, sore throat, or other signs of infection [119].**

**b) Physical Findings**

- 1) Obtain baseline ECG in patients with cardiac disease, elderly, or if initiating larger-than-usual doses. Repeat periodically during therapy if clinically warranted [119].**

**a) Depression**

- 1) 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 [199].

**2j)** 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 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 [199].

**b) Attention Deficit Hyperactivity Disorder (ADHD)**

**1j)** The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiograms (ECGs) or routine subspecialty cardiology evaluations (which were previously recommended by the American Heart Association (AHA) scientific statement to detect cardiac conditions that might place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity disorder ADHD in most children. The APA cited specific reasons for changing the recommendation including: lack of evidence establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher than that in the general population of children, and lack of cost-effective analysis to support ECG screening or special evaluation by pediatric cardiologist [1059].

**2j)** Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) consensus statements, the following cardiac monitoring recommendations have been established to assist clinicians in the evaluation of children treated with stimulant drugs, including imipramine, for ADHD [1059][1060]:

- Conduct a thorough examination prior to initiating imipramine therapy for a diagnosis of ADHD. Special attention should be given to symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine current use of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical findings associated with Marfan syndrome, and signs of irregular cardiac rhythms. Prolongation of QTc, PR, and QRS, tachycardia, and rarely sudden death have all been reported with imipramine use.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac disease during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist .

- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up visits.
- Blood pressure and heart rate should be evaluated at baseline, at dose increases, during routine follow-up within 1 to 3 months, and at follow up visits every 6 to 12 months.

## **B)) Imipramine** Pamoate

### **1)) Therapeutic**

#### **a)) Laboratory Parameters**

##### **1)) Dexamethasone Suppression Test (DST)**

**a))** The DST has been reported to be a useful tool in predicting whether or not a patient would respond to tricyclic antidepressant therapy (Brown et al, 1979, Brown et al, 1980). Eighty percent of patients with a positive DST responded to therapy versus a 37% response rate in patients with a negative DST [1049]. The usefulness of DST results as an indicator of tricyclic antidepressant therapy efficacy in the treatment of depression were not confirmed in one study [1050].

**b))** Depressed patients with abnormal DST may respond better to imipramine or desipramine therapy than amitriptyline or clomipramine therapy [1051]. The result of this study must be considered with caution since the investigator made a single evaluation of efficacy after 2 weeks of therapy. These results were not replicated utilizing imipramine and amitriptyline therapy [1052]. Therefore, DST results may not be a useful tool in the selection of a particular antidepressant.

##### **2)) Platelet Monoamine Oxidase Activity**

**a))** Measurements of platelet MAO activity with serotonin reveals that unmedicated depressed patients have a significantly higher degree of activity compared to controls. This degree of activity decreases progressively during imipramine therapy and falls within normal limits at the time the patient is classified as recovered [1053]. Whether platelet MAO activity is useful as a monitoring parameter remains to be determined.

##### **3)) Serum Concentrations**

**a))** Indications for determination of serum imipramine concentration [1058]:

- 1))** Utilization of adequate doses without experience clinical effect;
- 2))** Side effects uncertainly related to imipramine therapy;
- 3))** Monitoring high-dose imipramine therapy;

**4j)** Assess the influence of intercurrent illness on imipramine serum concentrations;

**5j)** Evaluating a patient suspected of intentional or unintentional overdose of imipramine.

#### **4j) Platelet Binding**

**a)** Imipramine has been shown to have specific high-affinity binding sites on human platelet membranes [1054]. These binding sites appear to be similar to those found in the human brain. Recent evidence indicates that platelet membrane binding may be decreased in some depressed patients [1054][1055][1056]; (Ambrusini et al, 1992). The exact value of this finding is still unknown; however, it may be of value in predicting which depressed patients are more likely to respond to antidepressant therapy.

**b)** The ability of the platelet to bind imipramine decreases with age. Whether this decrease in platelet binding is related to decreases in the density or number of receptors or an alteration in membrane microenvironment is unknown. Even though the decrease in platelet binding is significant, whether the changes effects the efficacy of the drug is unknown [1057].

**c)** Significant reductions in platelet imipramine binding have been observed in depressed patients. However, patients diagnosed with panic disorders or panic disorders concurrent with depression and patients with a previous history of depression have normal platelet imipramine binding compared to controls. The reason for this difference is unknown, but may indicate that the 2 syndromes differ neurochemically [1055].

#### **b) Physical Findings**

##### **1) Depression**

**a)** Clinical improvement of the signs and symptoms of depression.

##### **2) Attention Deficit Hyperactivity Disorder (ADHD)**

**a)** Improvement in mental and behavioral symptoms, including inappropriate inattention, impulsivity, hyperactivity, and cognitive performance.

#### **2) Toxic**

##### **a) Laboratory Parameters**

**1)** Obtain WBC and differential cells in patients with fever, sore throat, or other signs of infection [120].

**b) Physical Findings**

**1j)** Obtain baseline ECG in patients with cardiac disease, elderly, or if initiating larger-than-usual doses. Repeat periodically during therapy if clinically warranted [120].

**2j)** 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 [199].

**3j)** 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 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 [199].

**a) Attention Deficit Hyperactivity Disorder (ADHD)**

**1j)** The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiograms (ECGs) or routine subspecialty cardiology evaluations (which were previously recommended by the American Heart Association (AHA) scientific statement to detect cardiac conditions that might place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity disorder ADHD in most children. The APA cited specific reasons for changing the recommendation including: lack of evidence establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher than that in the general population of children, and lack of cost-effective analysis to support ECG screening or special evaluation by pediatric cardiologist [1059].

**2j)** Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) consensus statements, the following cardiac monitoring recommendations have been established to assist clinicians in the evaluation of children treated with stimulant drugs, including imipramine pamoate, for ADHD [1059][1060]:

- Conduct a thorough examination prior to initiating imipramine pamoate therapy for a diagnosis of ADHD. Special attention should be given to symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine current use of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical findings associated with Marfan syndrome, and signs of irregular cardiac rhythms.

Prolongation of QTc, PR, and QRS, tachycardia, and rarely sudden death have all been reported with imipramine pamoate use.

- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac disease during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up visits.
- Blood pressure and heart rate should be evaluated at baseline, at dose increases, during routine follow-up within 1 to 3 months, and at follow up visits every 6 to 12 months.

#### 4.2] Patient Instructions

##### A) Imipramine (By mouth)

##### Imipramine

Treats depression. May also be used to treat bedwetting in children. This medicine is a tricyclic antidepressant.

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an [allergic reaction](#) to [imipramine](#) or to related medicines such as [amitriptyline](#) (Elavil®), [carbamazepine](#) (Tegretol®), [maprotiline](#) (Ludiomil®), or [nortriptyline](#) (Aventyl®). You should not use this medicine if you have had a recent [heart attack](#) or have taken an MAO inhibitor such as [isocarboxazid](#) (Marplan®), [phenelzine](#) (Nardil®), [selegiline](#) (Eldepryl®), or [tranylcypromine](#) (Parnate®) in the past 14 days.

How to Use This Medicine:

Capsule, Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.

You may take this medicine with or without food.

Do not crush or chew the capsules. You may open the capsules and mix the medicine beads with soft food (pudding or applesauce). Swallow the mixture without chewing.

If you are taking this drug for depression, it may take 2 to 3 weeks before you start to feel better.

This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

If you take one dose a day at bedtime, you should not use the missed dose the next morning. Wait until your next regular bedtime dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.



Keep all medicine away from children and never share your medicine with anyone.

**Drugs and Foods to Avoid:**

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are using [atropine](#), [benztropine](#) (Cogentin®), [cimetidine](#) (Tagamet®), [guanethidine](#) (Ismelin®), [methylphenidate](#) (Ritalin®), [scopolamine](#), medicine for [high blood pressure](#) (such as [clonidine](#) or [Catapres®](#)), certain medicine for heart rhythm problems (such as [quinidine](#), [flecainide](#), [propafenone](#), Quinaglute®, [Tambocor®](#), or [Rythmol®](#)), medicine to treat seizures (such as [phenobarbital](#), [phenytoin](#), or [Dilantin®](#)), a phenothiazine medicine (such as [chlorpromazine](#), [perphenazine](#), [prochlorperazine](#), [promethazine](#), [thioridazine](#), [Compazine®](#), [Mellaril®](#), [Phenergan®](#), [Thorazine®](#), or [Trilafon®](#)), or other medicines to treat depression (such as [fluoxetine](#), [paroxetine](#), [sertraline](#), [Paxil®](#), [Prozac®](#), or [Zoloft®](#)).

Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.

Do not drink alcohol while you are using this medicine.

**Warnings While Using This Medicine:**

Make sure your doctor knows if you are pregnant, planning to become pregnant, or breastfeeding. Tell your doctor if you have [glaucoma](#), trouble urinating, mental problems, stomach problems, seizures, [heart disease](#), liver disease, [kidney disease](#), or thyroid disease.

For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your doctor or your child's doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has [bipolar disorder](#) (manic-depressive) or has tried to commit suicide.

Do not give this medicine to a child unless directed to do so by the child's doctor.

This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar ([hypoglycemia](#)).

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

Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.

This medicine may make your skin more sensitive to sunlight. Use a sunscreen when you are outdoors. Avoid sunlamps and tanning beds.

This medicine may cause dizziness and vision changes. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert or able to see well.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

**Possible Side Effects While Using This Medicine:**

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

[Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Anxiety, restlessness, nervousness, or mood or mental changes.

Change in how much or how often you urinate, or problems with urination.

Changes in behavior, or thoughts of hurting yourself or others.

Chest pain, shortness of breath, cold sweats, and bluish-colored skin.  
Fast, pounding, or irregular heartbeat.  
Lightheadedness or fainting when getting up suddenly from a lying or sitting position.  
Numbness or tingling in the hands and feet.  
Numbness or weakness in your arm or leg, or on one side of your body.  
Seizures or tremors.  
Sudden or severe headache, problems with vision, speech, balance, or walking.  
Swelling in your hands, ankles, or feet.  
Trouble sleeping.  
Twitching or muscle movements you cannot control.  
Unexplained fever or sore throat.  
Unusual bleeding or bruising.  
Unusual tiredness or weakness.  
Yellowing of your skin or the whites of your eyes.

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

Breast swelling or discharge.  
Changes in vision.  
Changes in weight.  
Dizziness or drowsiness.  
Dry mouth.  
Nausea, vomiting, diarrhea, constipation, or upset stomach.  
Problems having sex.  
Ringing in the ears.  
Skin rash or itching.  
Swelling of the breast or testicles in men.

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

#### 4.3] Place In Therapy

A) Depression is a complicated disorder and consequently this disease's treatment regimens are diverse. The two most prevalent diagnostic syndromes among affective disorders are [major depression](#) and [bipolar disorders](#). The tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs) are considered the most effective agents for treating [major depression](#). For treating [bipolar disorders](#), [lithium](#) is considered the standard of therapy over TCAs, MAOIs and other agents such as [carbamazepine](#) or [levothyroxine](#).

B) [Imipramine](#) and [amitriptyline](#), along with the selective serotonin reuptake inhibitors (SSRI) antidepressants, are considered the standard of therapy for endogenous or typical depression. In addition, [imipramine](#) may be employed for treating [agoraphobia](#). [Imipramine](#) has also been used adjunctively for pediatric [enuresis](#), adult [urinary incontinence](#) associated with [neurogenic bladder](#), [female stress incontinence](#), and geriatric spontaneous unstable detrusor contractions. Some studies indicate that chronic pain and [diabetic neuropathies](#) may also be alleviated with [imipramine](#). Although TCAs reportedly lower seizure threshold, [imipramine](#) has been demonstrated to reduce the frequency of absence and [myoclonic seizures](#). When an epileptic patient is refractory to other antidepressants and a TCA is deemed necessary for treatment, [imipramine](#) should be considered.

C) [Imipramine](#) and [amitriptyline](#) still have a place in therapy as the standards for the treatment of [major depression](#) along with the SSRI antidepressants. Newer classes of antidepressants are not more effective than [imipramine](#) for typical depression, but do offer alternatives for treating patients intolerant of TCAs or exhibiting [atypical depression](#). Being versatile, [imipramine](#) may be used in the therapy of other disorders besides depression and should be included on hospital formularies. Institutions that commonly treat depression should consider a diverse formulary with agents from each antidepressant class.

#### 4.4] Mechanism of Action / Pharmacology

##### A) MECHANISM OF ACTION

###### 1) DEPRESSION

a) The antidepressant mechanism of action of [imipramine](#) has not been completely determined but appears to be the result of interaction with biogenic amines. [Imipramine](#), like other tricyclic antidepressants, blocks the re-uptake of [norepinephrine](#) and 5-hydroxy-tryptamine at nerve terminals preventing their degradation and increasing their availability. This results in a decreased turnover of these amines in selective neurons but the relation of this effect to anti-depressant activity has not been demonstrated [1037]. Effects on the D1 [dopamine](#) receptor may also be important in the mediation of [imipramines](#) antidepressant activity [1038].

###### 2) ENURESIS

a) Why [imipramine](#) works in the treatment of [enuresis](#) is not well understood. Its beneficial effects do not appear to be related to changes in sleep architecture, anticholinergic properties, antiadrenergic properties, or effects on thyroid releasing hormone-induced urinary urgency. In patients with nocturnal polyuria, [imipramine](#) had a vasopressin-independent antidiuretic effect attributed primarily to increased tubular reabsorption of urea and to a lesser extent to decreased sodium and potassium excretion [1039]. The drug improves functional bladder capacity during chronic administration [1040][996].

##### B) REVIEW ARTICLES

1) A Consensus Statement on Panic Disorder is available from the International Consensus Group on Depression and Anxiety [1041]. Also an excellent review is available on the treatment of [panic disorder](#) [1042].

2) Drug-interactions of antidepressants are reviewed in German language [1043].

#### 4.5] Therapeutic Uses

##### 4.5.A] [Imipramine](#)

###### 4.5.A.1] [Anorexia nervosa](#)

See Drug Consult reference: [ANOREXIA NERVOSA - DRUG THERAPY](#)

###### 4.5.A.2] [Cataplexy - Narcolepsy](#)

See Drug Consult reference: [NARCOLEPSY AND CATAPLEXY - DRUG THERAPY](#)

###### 4.5.A.3] [Ophthalmoplegic migraine](#)

See Drug Consult reference: [THERAPY OF HEADACHE IN CHILDREN](#)

###### 4.5.A.4] [Severe major depression with psychotic features](#)

See Drug Consult reference: [PSYCHOTIC DEPRESSION - DRUG THERAPY](#)

#### 4.5.B] Imipramine Hydrochloride

##### 4.5.B.1] Agoraphobia

###### 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 the treatment of [agoraphobia](#) (Deltito et al, 1991)

Efficacy appears to be dose-related and usually requires doses of 150 milligrams or greater per day

###### c) Adult:

1) [Imipramine](#) and placebo were equally effective in the treatment of [agoraphobia](#) in a double-blind clinical trial combining drug therapy with brief psychological treatment [59]. The drugs were started 2 weeks prior to the initiation of the psychological therapy. At week 6 the mean dose of [IMIPRAMINE](#) was 124 milligrams and at week 14 it was 158 mg/day. During week 2 to week 12 each treatment group received 6 fortnightly sessions of therapist-aided relaxation. In addition each patient was given a leaflet describing the nature of [agoraphobia](#) and ways to cope with it. All patients were requested to complete systematic self-exposure homework and record these activities in a diary. Drug therapy was gradually withdrawn over weeks 26 to 28 of therapy. At the 2-year follow-up only 40 subjects were available. Five subjects had dropped out of the study (2 refused follow-up, 1 died, 1 moved out of the country, and 1 was untraceable). Two-thirds of the patients remained improved with regards to their phobias. There was no significant difference between those patients treated with [imipramine](#) or placebo therapy. Nor was there a superior effect of therapist-aided exposures over brief therapist-aided relaxation.

2) The plasma [IMIPRAMINE](#) levels, but not [DESIPRAMINE](#), correlated with the improvement in [agoraphobia](#) [60], which may indicate that the antiphobic effects of [IMIPRAMINE](#) therapy are mediated through a post-synaptic serotonergic neurotransmitter system and not the noradrenergic system.

3) [IMIPRAMINE](#) therapy plus programmed in vivo exposure practice was superior to [IMIPRAMINE](#) therapy alone [61][62].

##### 4.5.B.2] Anorexia nervosa

###### a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Has resulted in some improvement in patients with [anorexia nervosa](#)

**c) Adult:**

1) [Imipramine](#) treatment resulted in some improvement in 7 patients with [anorexia nervosa](#) treated serially with several antidepressants (tricyclics, MAOIs, and triazolopyridines) including [imipramine](#). Three of the patients received only [imipramine](#); the treatment trials ranged from 6 to 14 weeks. Four of the patients had some improvement in anorexic symptoms, 2 experienced some weight gain, and 3 of 3 who had bulimic symptoms reported improvement. Improvement in anorexic symptoms (3 to 6 weeks) was slower than the improvement observed in depression and anxiety (2 to 4 weeks) following tricyclic therapy [77]. Significant weight gain generally began after 2 to 3 months. Patients treated with [IMIPRAMINE](#) tended to tolerate the drug poorly and appeared to have an extraordinary sensitivity to the drugs anticholinergic side effects when compared to patients treated with [trazodone](#) or MAOIs [77]. This extraordinary sensitivity to the drug's side effects may be associated with their low body weight.

**4.5.B.3] [Attention deficit hyperactivity disorder](#), predominantly inattentive type**

**a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: Pediatric, Class III

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Stimulants (eg, [amphetamine](#), [methylphenidate](#)) are the drugs of choice in the treatment of [attention deficit disorder](#)

**c) Pediatric:**

1) [Imipramine](#) therapy should be considered an alternative or adjunctive agent when these agents fail or the patient is unable to tolerate them [72][15]. The dose used ranges from 25 to 100 milligrams/day and tends to be lower than those needed to treat depression. Children tend to respond within 24 hours after initiating therapy. The monitoring of serum [imipramine](#) and [desipramine](#) levels may be useful. The serum levels associated with reported responses have been 10 to 54 ng/ml of [imipramine](#) and 10 to 65 ng/ml of [desipramine](#) [73].

2) A 6-year-old retarded child with [Fragile X syndrome](#) and [attention deficit disorder](#) responded to [IMIPRAMINE](#) therapy [72]. [IMIPRAMINE](#) improved the boy's insomnia, [enuresis](#), and [attention deficit disorder](#), whereas, previous therapy with [METHYLPHENIDATE](#) had caused a deterioration in behavior.

3)) A 12-year-old boy with a history of severe [attention deficit disorder](#) and stimulant-induced [Tourette's syndrome](#) responded well to [IMIPRAMINE](#) therapy (50 milligrams/d). During the course of [IMIPRAMINE](#) therapy the [attention deficit disorder](#) substantially improved and the Tourette's symptomatology was not affected [74].

4)) Ten hyperactive children were treated with [IMIPRAMINE](#) 75 to 150 milligrams/day and no response was detected in any of the patients [75].

5)) Fifty-two children, 3 to 14 years of age, were enrolled in an open clinical study to evaluate the efficacy of [IMIPRAMINE](#) in the treatment of CHILDHOOD HYPERACTIVITY [76]. Thirty-five of the 52 children (67%) showed a marked improvement in behavior. The average daily dose of [IMIPRAMINE](#) was 50 mg (25 to 125 mg). Sixty-five percent (11/17) of the children failing to respond to [IMIPRAMINE](#) therapy subsequently responded to [METHYLPHENIDATE](#) therapy.

#### 4.5.B.4] [Binging](#)

##### 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 beneficial for weight loss when added to diet counseling and psychological support in obese binge eaters

##### c)) Adult:

1)) A short course of low dose [imipramine](#) added to diet counseling and psychological support helped obese binge eaters to lose weight and maintain their weight loss. In a double-blind study, binge eaters (as defined by DSM-IV criteria) with a body mass index of greater than 27.5-kilograms (kg)/square meter randomly received [imipramine](#) 25 milligrams 3 times daily (n=15) or placebo (n=16) for 8 weeks. Diet counseling and psychological support were provided during the medication phase and continued for 6 months thereafter. [Imipramine](#)-treated patients experienced a weight loss of 2.2 kg while the placebo group remained stable (p=0.0002). The occurrence of depression was low for both groups; however, mean scores on the Hamilton Depression scale declined in the [imipramine](#) group (p less than 0.001) but not in the placebo group. Binge eating episodes declined from 7.1 episodes/week to 2.8 episodes for the [imipramine](#) group (p less than 0.001) and from 7.1 episodes to 5.4 episodes in the placebo group (p not significant). After the active treatment phase, [imipramine](#) patients continued their weight loss by a mean of 1.9 kg (p less than 0.001) while placebo- treated patients regained weight (p not significant) [79].

#### 4.5.B.5] [Bulimia nervosa](#)

##### 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:**

Approximately 75% of patients show at least a moderate response (reduction of binge eating by 50%) to antidepressant therapy

Monoamine oxidase inhibitors also appear effective in [bulimia](#), and may be superior to tricyclic antidepressants (Pope et al, 1983)

**c) Adult:**

1) Twenty bulimic subjects were followed for a period of up to 2 years to assess the long term efficacy of [IMIPRAMINE](#) therapy [64]. At the end of the follow-up period, 95% had at least partial improvement and 50% had experienced a complete remission. Over the course of the study period 85% had either maintained or improved upon the quality of their initial response. The one patient that failed to respond discontinued her medication and promptly relapsed to her original frequency of binge eating.

2) A retrospective study of 22 patients with [bulimia](#) treated with antidepressants ([AMITRIPTYLINE](#), [IMIPRAMINE](#), [DESIPRAMINE](#), [DOXEPIN](#), [TRAZODONE](#), [TRANLYCYPROMINE](#), or [PHENELZINE](#)) showed a decreased incidence of bingeing and/or an improvement in depression [65]. During a 3-month follow-up period several patients relapsed despite continuation of their antidepressant therapy, while others continued to benefit from drug therapy.

#### 4.5.B.6] [Cardiac dysrhythmia](#)

**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:**

Some patients with [ventricular tachycardia](#) or [premature ventricular contractions](#) may benefit from [imipramine](#) therapy

**c) Adult:**

1) [IMIPRAMINE](#) was included in a double-blinded crossover pilot study to evaluate the efficacy of [ventricular premature complex \(VPC\)](#) suppression after acute [myocardial infarction](#) as a means to improve survival [23]. Each patient was assigned to [ENCAINIDE](#), [FLECAINIDE](#), [IMIPRAMINE](#), [MORICIZINE](#), or placebo. The dose of the medication was adjusted to achieve 70% or greater reduction of [VPC](#) and greater than 90% reduction in unsustained [ventricular](#)

**tachycardia**. If the patient failed to achieve an adequate response or was unable to tolerate the drug, the drug was discontinued and they were crossed over to a different antiarrhythmic class (class 1C to class 1A or class 1A to class 1C). **ENCAINIDE** (79%) and **FLECAINIDE** (83%) were superior to **IMIPRAMINE** (52%), **MORICIZINE** (66%), and placebo (37%) as first line-drugs. In patients failing **IMIPRAMINE** or **MORICIZINE** therapy, **ENCAINIDE** was 68% and **FLECAINIDE** 69% effective. It would appear that **IMIPRAMINE** is not the drug of choice for the prevention of **VPC** following an acute **myocardial infarction**. In addition, changes in therapy secondary to the development or worsening of **congestive heart failure** occurred in 26% of the treatment groups compared to 18% in the placebo group [80].

2) **IMIPRAMINE** in doses of 50 to 400 milligrams/day (mean = 210 +/- 103 mg/day) and **NORTRIPTYLINE** in doses of 75 to 150 mg/day (mean = 100 +/- 29 mg/day) were effective in the reduction of PVCs [81]. Seventy percent of the patients had a greater than 80% suppression of their PVCs. Neither drug significantly changed mean ejection fraction or peak systolic pressure end-systolic volume ratio. Both drugs produced a reduction in standing systolic blood pressure.

3) Twenty-two patients with 30 or more **ventricular premature complexes** (PVCs) per hour were treated with oral **IMIPRAMINE** 1 milligrams/kilogram/day (in two divided doses), increasing by 1 mg/kg/day every other day until PVCs were suppressed by at least 80% (or until adverse effects were observed or a daily dose of 5 mg/kg/day was administered). Eighteen patients (82%) exhibited antiarrhythmic effects from **IMIPRAMINE** therapy. All patients treated did not have psychological depression. The elimination half-life was approximately 8 hours, however, duration of action of the drug was much longer and antiarrhythmic effects were observed over at least a 12 hour period, which suggests that metabolites of **IMIPRAMINE** may contribute to the duration of antiarrhythmic efficacy [82].

4) In patients with **premature ventricular contractions**, **IMIPRAMINE** was noted to suppress **arrhythmias** by greater than 90% in 10 of 11 patients. **IMIPRAMINE** shortens action potential duration and decreases conduction velocity and maximal velocity and therefore is classified as a class 1 antiarrhythmic drug. Since the half-life of **IMIPRAMINE** is relatively long (12 to 18 hours) it may be dosed on a twice daily regimen. Antiarrhythmic doses appear to be similar to antidepressant doses (3.5 mg/kg/day). The antiarrhythmic activity of **IMIPRAMINE** is partially attributed to its metabolites, desmethyylimipramine and 2-hydroxyimipramine. Due to complications, **IMIPRAMINE** should not be used in patients with pre-existing conduction defects [83].

#### 4.5.B.7] Depression

##### FDA Labeled Indication

##### a) Overview

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive

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:

Indicated for the relief of symptoms of depression [1]

[Endogenous depression](#) may be more likely to respond to [imipramine](#) therapy than other depressive states [1]

**c) Adult:**

1) Various depressive illnesses have responded to treatment with [IMIPRAMINE](#) in daily doses of 75 to 250 milligrams [2][3][4][5][6][7]; (Lindberg et al, 1979)[8]. Patients suffering from [endogenous depression](#) [7], non-endogenous depression (Lindberg et al, 1979), depression of [myotonic dystrophy](#) [9], [neurotic depression](#) [10] alcoholic patients with primary depression [11], and opiate-dependent patients with [depressive disorders](#) [12] may benefit from [IMIPRAMINE](#) therapy. However, the combination of [IMIPRAMINE](#) and a neuroleptic are effective in the treatment of delusional depression [13].

2) High dose tricyclic antidepressant therapy ([IMIPRAMINE](#) 150 to 200 milligrams/d, DESMETHYLIMIPRAMINE 150 to 500 mg/d) was effective in only a small portion of elderly patients with delusional depression. The dropout rate secondary to side effects was 58% and the overall success rate was only 25% [14].

**d) Pediatric:**

1) [IMIPRAMINE](#) is efficacious in the treatment of depression in children [15][16]. A general overview of the treatment of childhood behavioral and emotional disorders has been published [15].

2) [IMIPRAMINE](#) therapy in adolescents with major [depressive illness](#) was less effective than in adults in an open-label trial of 35 patients [17]. Twenty-four females and 11 male depressed patients between 13 and 18 years of age with a Hamilton Rating Scale for Depression scores of 16 or greater were enrolled in the study. Following a 7-day washout period, patients received [IMIPRAMINE](#) 5 milligrams/kilogram/day (up to a maximum of 300 mg) for 6 weeks. Thirty-four adolescents completed the trial. The average daily dose was 222 mg/day. Overall efficacy was low, with the ten patients with delusional subtypes responding more poorly than the nondelusional patients. Eight of the 24 nondelusional patients displayed delayed onset of response, followed by sustained improvement. Only one delusional patient demonstrated clinical improvement. Steady state plasma levels did not vary between responders and nonresponders. The results of this study suggest that [imipramine](#) may be less efficacious in the treatment of [major depression](#) in adolescents than in adults, as has previously been suggested for other tricyclic antidepressants, and raises questions about age differences in neurotransmitter and neuroregulatory system responses to specific antidepressant agents.

3) Twenty-one children (ages 5.8 to 10.25 years) with various types of depression were treated with [IMIPRAMINE](#) WITH 67% of the children showing some improvement [18]. The dose of [IMIPRAMINE](#) was started at 25 mg at bedtime and slowly increased over a period of 7 to 14 days to a maximum dosage of 5 milligrams/kilogram/day or 200 mg/day (one older child was treated with 225 mg/d (4.9 mg/kg/day)). Seven (33%) of the children experienced either a worsening or no significant change in any of the areas monitored. In fact, 2 children showed a significant increase in anger and hostility during the [IMIPRAMINE](#) therapy.

4) [Imipramine](#) was efficacious in the treatment of 20 prepubertal children hospitalized for [major depressive disorder](#) (DSM-III) with [imipramine](#) [19]. [IMIPRAMINE](#) therapy consisted of 75 milligrams/day, administered at bedtime, for the first 3 weeks and increased to a maximum of 5 milligrams/kilogram if no response. Serum [IMIPRAMINE](#) and [DESIPRAMINE](#) levels were

drawn during each phase of the study. During phase I, none of the 15 children with a total tricyclic antidepressant (TCA) plasma concentration outside the 125 to 225 ng/mL range showed a remission or improvement in their condition. Eighty percent of those children with serum levels between 125 to 225 ng/mL experienced a remission. During phase II, 12 of the 16 children achieved steady-state total TCA plasma concentrations of 125 to 225 ng/mL and 11 (92%) of them had experienced a remission by the end of the treatment period. Based on these results it can be concluded that **IMIPRAMINE** is effective in the treatment of depression in prepubertal children and its effectiveness is concentration-dependent.

#### 4.5.B.8] Diabetic neuropathy

##### a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

##### b) Summary:

Effective for **diabetic neuropathy** in selected patients

##### c) Adult:

1) In most patients, an **imipramine** plasma drug concentration of 400 to 500 nmol/L was sufficient to achieve maximal relief in the treatment of **diabetic neuropathy** [69]. All patients were diabetic and had one or more symptoms (pain, paresthesia, dysesthesia, and hypesthesia) and signs (reduction of sensibility, strength, or tendon reflexes) of **peripheral neuropathy**. One patient demonstrated no significant improvement even with **IMIPRAMINE** plus **DESIPRAMINE** levels below 400 nmol/L. In the other eleven patients doses of 125 to 350 milligrams/day were required to increase the levels to about 400 mmol/L. One patient required a blood level of 730 mmol/L to achieve maximal relief.

2) A double-blind, cross-over comparison of **IMIPRAMINE** with placebo was conducted in nine patients with symptomatic **peripheral diabetic neuropathy** [70]. The dose of **IMIPRAMINE** was adjusted to achieve a plasma **IMIPRAMINE** plus **DESIPRAMINE** level of 300 to 750 nmol (125 to 225 milligrams/day) during the first week. Each treatment period was three weeks and no washout phase was used between treatment periods. Efficacy was assessed at the end of each treatment period based on symptoms and measurement of peripheral and autonomic nerve function. **IMIPRAMINE** provided significant beneficial symptomatic improvement in all patients, but not beneficial changes in peripheral or autonomic nerve function.

3) **IMIPRAMINE** in doses of 50 milligrams (mg) daily for one week, then 100 mg daily for 4 weeks, was effective in producing improvement in 7 of 12 patients with severe **diabetic neuropathy** of the lower extremities in a double-blind, cross-over study [71]. **IMIPRAMINE** had beneficial effects on pain, paresthesia, dysesthesia numbness, and nocturnal aggravation.

#### 4.5.B.9] Disorder of ejaculation

##### a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

In case reports, [imipramine](#) has been effective in treating ejaculatory disorders

**c) Adult:**

**1) IMIPRAMINE** 25 milligrams three times/day corrected RETROGRADE EJACULATION of 18 months and 2 years duration in 2 adult diabetics. One patient had normal gonadotropin levels; the other had low plasma [testosterone](#) but [testosterone](#) therapy did not correct retrograde ejaculation [86].

**2) A** 29-year-old male with [ASPERMIA](#) of 4 years duration secondary to [lymphadenectomy](#) noted ejaculate of normal volume and consistency 1 day after beginning [IMIPRAMINE](#) 50 milligrams daily for depression. Motile spermatozoa were seen on microscopic examination and sperm count was 115,600,000/mm(3). [Aspermia](#) returned within 2 days of discontinuing [IMIPRAMINE](#) therapy. These results recurred on 3 separate occasions [87].

**4.5.B.10) Drug dependence**

**a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Has little effect in the treatment of drug addiction

Does improve mood in drug-addicted patients with [depressive disorders](#)

**c) Adult:**

**1) Treatment of depressed METHADONE-MAINTENANCE OPIATE ADDICTS** with [IMIPRAMINE](#) or a placebo resulted in similar subjective results in one study [84]. At the end of 8 weeks of therapy both groups had a substantial reduction in depressive symptoms. However, a 12-week, double-blind trial that excluded initial placebo responders during a pre-randomization period found significantly improved depression rating scores after treatment with [imipramine](#) (n=42) compared to placebo (n=42) (p less than 0.001). [Imipramine](#) doses were titrated based on response to a mean high dose of 268 milligrams daily [12].

2j) Imipramine had little effect in the treatment of COCAINE DEPENDENCE and METHAMPHETAMINE ABUSE in 183 patients (151 cocaine dependent and 32 methamphetamine dependent) seen at the Haight-Ashbury Free Clinics [85]. Patients were randomly assigned to treatment with imipramine 10 or 150 milligrams/day for up to 180 days in this double-blind study. In addition, all subjects were given intensive drug abuse counseling during the course of the treatment. Efficacy was based on negative urine samples, self reporting of abstinence, craving, and Beck depression inventory. The longest retention in the program occurred with the group receiving the higher imipramine dose (median retention 34 days vs 17 days). No differences in craving or depressive symptoms were observed and the depression scores in both groups decreased after the start of therapy. Positive urine analyses were less in the high dose imipramine group (5% vs 14%) at 14 days, but were no different at 28 or 90 days. Based on these results it appears that imipramine is of limited value in the treatment of cocaine or methamphetamine dependent patients who do not have a depressive disorder.

#### 4.5.B.11] Gardner-Diamond syndrome

##### a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Effective only for short-term therapy of autoerythrocyte sensitization

##### c) Adult:

1j) A 20-year-old female with autoerythrocyte sensitization and depression was treated with IMIPRAMINE therapy [78]. One week later the bleeding resolved and after 2 weeks the depression began to resolve. In 3 to 4 weeks all symptoms had resolved. Six weeks later, while still receiving therapeutic doses of IMIPRAMINE, the depressive symptoms recurred and 10 days later bleeding restarted. Compared to previous episodes the severity of depression and bleeding was less severe. The bleeding resolved in 10 days and the depressive symptoms were gone within 6 weeks. Following a subsequent relapse in therapy the IMIPRAMINE was discontinued and AMITRIPTYLINE therapy (300 mg/d) was initiated. Since the start of AMITRIPTYLINE therapy the patient has been free of depression and bleeding for 10 months.

#### 4.5.B.12] Globus hystericus

##### 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:**

Efficacy demonstrated in case reports only

**c) Adult:**

**1) [Globus hystericus](#)** syndrome is a condition in which the individual develops a fear that he/she is intermittently choking and unable to breathe. If the condition is left untreated the patient may become profoundly disabled or may develop a life-threatening weight loss. Case reports of three patients have shown that psychoactive drugs may be effective in controlling this condition. [IMIPRAMINE](#) therapy was effective in the treatment of one case, [PHENELZINE](#) in another, and [TRANLYCYPROMINE](#) in the other case [89]. Two additional cases of successful [imipramine](#) treatment of [globus hystericus](#) syndrome were reported [90][91].

**4.5.B.13] Mood swings**

**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:**

Possibly effective for PATHOLOGICAL CRYING/LAUGHING

**c) Adult:**

**1) Heightened tendency for crying or laughing in frequency and inappropriate circumstances** (pathological crying or laughing) and emotional lability unrelated to depression can occur in individuals with brain damage (eg, [stroke](#) patients). Small doses of [IMIPRAMINE](#) (30 to 60 milligrams) may partially or completely control the emotionalism within weeks [88].

**4.5.B.14] Nocturnal enuresis**

FDA Labeled Indication

**a) Overview**

FDA Approval: Adult, no; [Pediatric, yes \(6 years and older\)](#)

Efficacy: Pediatric, Effective

Recommendation: Pediatric, Class IIa

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Indicated as temporary adjunctive therapy for the reduction of [enuresis](#) in children 6 years and older [1]

**c) Pediatric:**

**1)** Numerous double-blind, crossover, placebo-controlled studies have demonstrated [IMIPRAMINE](#)'s effectiveness as adjunct treatment of [enuresis](#) in pediatric patients. Most studies report the use of doses ranging from 10 to 50 milligrams administered at bedtime although doses as high as 100 mg have been utilized. The application of pharmacokinetic data (ie, Bayesian methods) may improve the individualization of [IMIPRAMINE](#) dosing in the treatment of [enuresis](#) [26][27][28]. Most studies report only minor side effects including dry mouth, constipation, irritability, anorexia, and sleep disturbances [2][29][30][31][32][33][34][35][36][37].

**2)** Follow-up of 29 young adults, 10 years after [IMIPRAMINE](#) therapy for [enuresis](#), suggests that no psychological harm results from this therapy; these patients showed no psychological decompensation, inhibition of learning or predisposition to drug abuse [38].

**4.5.B.15] Obsessive-compulsive disorder**

**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:**

Questionable efficacy in the treatment of [obsessive-compulsive disorder](#)

**c) Adult:**

**1)** [Imipramine](#) was ineffective in treating [obsessive-compulsive disorder](#) (OCD) in a double-blind, placebo-controlled study that evaluated the efficacy of [IMIPRAMINE](#) in the treatment of depression and obsessive-compulsive symptoms in 37 patients [92]. Nineteen (10 women and 9 men) were treated with [IMIPRAMINE](#) and 18 (9 women and 9 men) were treated with a placebo. Each placebo patient received 10 tablets per day. The [IMIPRAMINE](#) group was started and increased by 25 mg every other day until clinical response, side effects, or a maximum daily dose of 250 mg. The average daily [IMIPRAMINE](#) dose was 233 mg (150 to 250 mg). At the end of 6 weeks the [IMIPRAMINE](#) was effective in reducing symptoms associated with depression, but had little to no effect on their obsessive-compulsive symptoms.

**2)** Four patients with obsessive-compulsive bowel obsessions were treated with [IMIPRAMINE](#) (3) or [DOXEPIN](#) (1). All 4 patients were free of their bowel obsession within 30 days (10, 14, 14, 30) of starting drug therapy (Jenike et al, 1987).

**4.5.B.16] Pain**

**a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Pain has occasionally resolved with [imipramine](#) therapy

**c) Adult:**

**1)** Patients with chest pain, but normal [coronary angiograms](#), may respond to [imipramine](#) therapy [93]. The dose of medications used in the study were [imipramine](#) 50 milligrams at night and placebo in the morning, [clonidine](#) 0.1 milligrams twice daily, and placebo twice daily. The incidence of chest pain was decreased by 52 +/- 25% compared with 1 +/- 86% with placebo and 39 +/- 51% with [clonidine](#) therapy (data is presented as means +/- SD). Only pain relief associated with [imipramine](#) use was statistically significant (p=0.03). A follow-up evaluation of these patients, over an average of 21 months, indicated that none of the patients had been seen in an emergency room or had been hospitalized because of chest pain. Seventeen patients have had the [imipramine](#) therapy discontinued and 16 asked to resume the [imipramine](#) therapy because of recurrent chest pain symptoms [94]. The mechanism of this pain relief is unknown, but may be a result of a visceral analgesic effect and not dependent on cardiac, esophageal, or psychiatric characteristics or gender. Another possible mechanism for this effect may be an increased pain threshold resulting from the reduction in psychological depression [95].

**2)** A survey of Italian oncology centers revealed that 43% of their patients were given antidepressants. The most frequently utilized drugs were [AMITRIPTYLINE](#), [CLOMIPRAMINE](#), [IMIPRAMINE](#), and [TRAZODONE](#). Most physicians felt that the antidepressants were useful in controlling pain and were most efficacious in depressed patients [96].

**3)** A case report of a 26-year-old graduate student being treated with [IMIPRAMINE](#) for suicidal thoughts and low self-esteem noted an improvement in her chronic pelvic pain (induced by [endometriosis](#) four years earlier) while on [IMIPRAMINE](#) therapy [97].

**4.5.B.17) [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:**

Similar in efficacy to [alprazolam](#)

**c) Adult:**

## 1J) GENERAL INFORMATION

- aJ) The clinical response to **IMIPRAMINE** in the treatment of **panic disorder** is independent of the presence of depression or **dysphoria** [40]. Patients with high baseline depression scores have tended to have the poorest outcomes [41][42][43][44]. Maintenance with half-dose **IMIPRAMINE** therapy may be useful in providing patients with a protective effect against **relapses** [45][46]. The use of **IMIPRAMINE** in the treatment of **panic disorder** may not be as safe as other anxiolytics in patients with **cardiovascular disease** [47].
- 2J) Combination **imipramine** and **cognitive-behavioral therapy** (CBT) was of limited value initially but provided advantages during maintenance therapy in patients with **panic disorder**. Patients with **panic disorder** randomly received CBT alone (n=77), **imipramine** alone (n=83), placebo alone (n=24), CBT with **imipramine** (n=65), or CBT alone (n=63) for a 12- week acute treatment phase. Thereafter, responders entered a 6-month maintenance phase. Patient responses were evaluated following the 12- week acute treatment phase, the 6-month maintenance phase, and 6-months after therapy discontinuation; assessment tools included the **Panic Disorder Severity Scale** (PDSS) and the **Clinical Global Impression Scale** (CGI). Initial **imipramine** doses were 10 milligrams (mg)/day slowly increased over 5 weeks to 200 mg and further increased to 300 mg if symptoms continued. Following acute treatment, responses for the PDSS were 48.7% for CBT alone, 45.8% for **imipramine** alone, 21.7% for placebo alone, 60.3% for CBT with **imipramine**, and 57.1% for CBT plus placebo. Both CBT alone and **imipramine** alone were significantly better than placebo (p=0.03 and p=0.05, respectively), however, combination therapy provided no greater response rate over each treatment alone (p not significant). For the CGI during the acute phase, none of the therapies were significantly better than the others. Following maintenance therapy, responses on the PDSS were 39.5% for CBT alone, 37.8% for **imipramine** alone, 13% for placebo alone, 57.1% for CBT with **imipramine**, and 46.8% for CBT plus placebo. Responses on both the PDSS and the CGI were significantly better for **imipramine** versus placebo (p=0.02 for both) and CBT versus placebo (p=0.02, p=0.01, respectively). Using the PDSS, the combination therapy was significantly better than either CBT alone (p=0.04) and better than **imipramine** alone (p=0.03). On the CGI, combination therapy was only significantly better than **imipramine** alone (p=0.03) and not better than CBT alone (p not significant). Following treatment discontinuation after the 6-month maintenance phase, the only statistical difference was the PDSS scores in the CBT group compared to the placebo group (p=0.05) [48].
- 3J) Maintenance treatment with **imipramine** had a significant protective effect against **relapse** in patients with **panic disorder** and **agoraphobia**. Patients who had shown an initial good and stable response to **imipramine** therapy over 24 weeks randomly received same-dose **imipramine** continuation (n=29) or placebo discontinuation (n=27). Patients continued their initial **imipramine** at a target dose of 2.25 milligrams/kilogram or discontinued their **imipramine** by decreasing the dose by 25% each week (substituted with placebo). During this study, no patient received behavioral or cognitive instructions unless a crisis-type intervention was needed. During the study, if **relapse** was confirmed the patient exited the study; **relapse** was defined as a worsening of their condition (measured as a 33% decline in the End- State Function scale score) accompanied by insistent requests for therapeutic action. After 12 months, the study population consisted of 20 patients in the **imipramine** group and 10 patients in the placebo group. This resulted in a 92.5% lower hazard rate of **relapse** with **imipramine** as compared to placebo [49].

4)) In a double-blind study, an 8-month therapy period for [panic disorder](#) with either [alprazolam](#) or [imipramine](#) was effective [50]. Patients received [alprazolam](#) (n=37), [imipramine](#) (n=34), or placebo (n=35) during an 8-week period of short-term treatment, a 6-month maintenance period, and then a 15-month follow-up period. Patients receiving [alprazolam](#) began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving [imipramine](#) began at 25 mg and were increased to 250 mg. [Alprazolam](#) patients had notable reductions in panic attacks during the first 2 weeks of therapy while [imipramine](#) patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates during this time were 11% in the [alprazolam](#) group, 41% in the [imipramine](#) group, and 57% in the placebo group (p less than 0.001 for [alprazolam](#) versus the other groups). In the remaining patients it was noted that tolerance developed to adverse effects during the maintenance phase. After the 6-month maintenance phase, doses were titrated off over 3 weeks. At this point, 62% of the [alprazolam](#) and 26% of the [imipramine](#) groups were panic-free (p less than 0.01). During the follow-up period, patients could be treated with non-study medications. Regardless of medication, patients who completed 8 months of treatment were more likely to be panic-free than those who had dropped out, even if they received non-study medications (85% versus 55%, p less than 0.01). Remission rates were higher in younger patients, those with a history of more frequent or intense panic attacks, those with a lower initial phobia score, and those with an initial lower score of inadequacy, low self-confidence, and passivity (Minnesota Multiphasic Personality Inventory Dependency Scale).

5)) A comparison of [cognitive therapy](#), applied relaxation, and [imipramine](#) found that at 3 months [cognitive therapy](#) was superior to both applied relaxation and [imipramine](#) therapy [51]. At 6 months the [cognitive therapy](#) and [imipramine](#) treatment produced similar results and were better than applied relaxation. However, between the 6th and 15th months of therapy, several of the [imipramine](#) patients relapsed while the patients treated with [cognitive therapy](#) continued to do better than with [imipramine](#) and relaxation therapy.

#### 4.5.B.18| [Posttraumatic stress disorder](#)

##### a)) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### b)) Summary:

Resulted in improvement in positive symptoms of [post-traumatic stress disorder](#)

##### c)) Adult:

1)) [Imipramine](#) treatment resulted in improvement in positive symptoms of [post-traumatic stress disorder](#) (PTSD) in 10 patients [98]. Therapy was initiated at a low dose and increased over the following 7 days to the highest tolerable dose (mean 260 milligrams/day; range 50 to 350 mg/d). After 2 to 3 weeks of therapy, there was a significant decrease in the severity of forced recollection, sleep and dream disturbances, and a cessation or reduction in flashbacks. Most avoidance items, eg, staying away from reminders of the event, trying not to talk about the event, and trying to

remove it from their memory, did not decrease significantly in severity. Based on these results it would appear that [IMIPRAMINE](#), in combination with psychotherapy, may be an effective treatment for patients.

2) Treatment of 3 patients with [acute post-traumatic stress disorder](#) (PTSD) with either [DOXEPIN](#) or [IMIPRAMINE](#) resulted in an improvement in PTSD symptoms [99]. Whether or not tricyclic antidepressant therapy is superior, equivalent, or inferior to psychotherapy or other means of treatment remains to be determined.

#### 4.5.B.19| Schizophrenia; Adjunct

##### a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIb; [Pediatric, Class III](#)

Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### b) Summary:

May be effective as adjunct therapy in depressed schizophrenic patients

Ineffective for [schizophrenia](#) itself

##### c) Adult:

1) Schizophrenic or schizoaffective patients with POSTPSYCHOTIC DEPRESSION may benefit from the addition of [IMIPRAMINE](#) to their [neuroleptic therapy](#). Favorable results were observed in 27 patients previously treated with [FLUPHENAZINE](#) DECANOATE and [BENZTROPINE](#) after the addition of [IMIPRAMINE](#) to their drug regimen. These beneficial effects continued in those patients with postpsychotic depression that initially responded to the addition of [IMIPRAMINE](#) to their regimen and were monitored for an additional six months on the triple drug regimen (n=23). The four patients that did not complete the six-month observation period were discontinued for administrative reasons and none had a [relapse](#) in either [psychosis](#) or depression [100]. A one-year follow-up study documented the clinical value of maintaining [imipramine](#) therapy in the treatment of postpsychotic depression [101].

2) A preliminary study indicates that [imipramine](#) may be an effective adjunctive agent in the acute treatment of substance-abusing dysphoric schizophrenic or schizoaffective patients [102]. The importance of these results remain to be proven.

##### d) Pediatric:

1) A pilot study in 10 autistic and schizophrenic children age 2 to 6 years found [IMIPRAMINE](#) therapy to be ineffective [103]. The drug did decrease affective blunting, anergy, and withdrawal and stimulated speech production in several children, but increased psychotic speech, behavioral disorganization, and excitation in other children.

#### 4.5.B.20| Separation anxiety disorder of childhood

##### a) Overview



FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: **Pediatric, Class III**

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Routine use of tricyclic antidepressants is not recommended for separation anxiety in children. [Behavioral therapy](#) may be just as effective as [imipramine](#).

**c) Pediatric:**

**1)** The combination of [imipramine](#) and nonpharmacologic therapies (eg, parent management training, behavior therapy, and family therapy) may improve subjective comfort, reduce anxiety and somatic symptoms in 70% of the children experiencing separation-anxiety disorder [15]. This disorder is associated with a high rate of spontaneous recovery, therefore the routine use of tricyclic antidepressants is not recommended [15].

**2)** Both [IMIPRAMINE](#) and placebo therapy were equally effective for separation anxiety. A small, double-blind, randomized placebo-controlled study was conducted with 21 children with separation anxiety disorder [105]. All the children were first given a month of vigorous [behavioral treatment](#), then randomly assigned to [IMIPRAMINE](#) or placebo therapy for six weeks. Both treatments were approximately 50% effective.

**4.5.B.21] Sexual disorder**

**a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Effective in case reports only

**c) Adult:**

**1)** [IMIPRAMINE](#) may be useful, alone or in combination with [LITHIUM](#), in the treatment of men with [PARAPHILIAS](#) or NONPARAPHILIC SEXUAL ADDICTIONS [106]. Two patients with sexual disorders improved following [IMIPRAMINE](#) therapy. Whether [IMIPRAMINE](#) and other antidepressants are useful in the treatment of all males with [paraphilias](#) or nonparaphilic sexual addictions or just specific types remains to be determined.

**4.5.B.22] Sleep 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:**

Used successfully in the treatment of NIGHT TERRORS, SOMNABULISM, [NARCOLEPSY](#), and [CATAPLEXY](#)

**c)) Adult:**

1)) [IMIPRAMINE](#) therapy (50 to 100 milligrams at bedtime) resulted in a dramatic reduction in frequency and severity of night terrors in 2 patients unresponsive to [DIAZEPAM](#) therapy [107].

2)) [IMIPRAMINE](#) therapy resulted in a significant reduction (242 +/- 156 to 142.8 +/- 120.1) in the total number of apneic episodes in 41.9% of the patients tested [108]. Based on these results it appears that [IMIPRAMINE](#) therapy may be an alternative form of therapy for some nonoverweight patients with negative ear, nose and throat (ENT) findings and for some patients who had not responded to weight reduction or ENT surgery.

3)) A 62-year-old female had suppression of night terrors with [IMIPRAMINE](#) 50 milligrams at bedtime; 75 mg had completely suppressed night terrors but caused daytime drowsiness (Beitman & Carlin, 1979).

**4.5.B.23] [Social phobia](#)****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:**

No studies currently support the use of [imipramine](#) for [social phobia](#)

**c)) Adult:**

1)) [Imipramine](#) was not useful in the treatment of [social phobia](#) in an 8-week, open-trial of 15 patients [109]. [Imipramine](#) was started at 50 milligrams (mg) for 3 nights and increased at weekly intervals to a maximum dose of 300 mg by the fourth week. Only 9 patients were able to complete the study as the others dropped out due to adverse effects. Only 2 patients responded to [imipramine](#) therapy as determined by the Liebowitz Social Anxiety Scale and Liebowitz [Social](#)

[Phobia](#) Disorders Scale-Overall Severity. They were also unable to continue further therapy as 1 developed urinary hesitancy and the other became hypomanic.

#### 4.5.B.24] Trichotillomania

##### a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: [Pediatric, Class IIb](#)

Strength of Evidence: Pediatric, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### b) Summary:

Used successfully in a case of [trichotillomania](#) and depression in a pediatric patient [110].

#### 4.5.B.25] Urinary incontinence

##### a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive

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:

Used alone or in combination with other anticholinergic medications, can improve urinary continence

May not be better than [bladder training](#) in some patients

May help to achieve continence in children with [myelodysplasia](#) alone or in combination with [oxybutynin](#)

##### c) Adult:

1) [Imipramine](#) was useful for genuine stress continence. In a prospective study, women with [genuine stress incontinence](#) received [imipramine](#) 25 milligrams 3 times daily for 3 months. A urodynamic assessment was done with a 20-minute pad test to determine the amount of urine leakage. A cure was defined as a pad weight that resulted in 0 grams after treatment. After 3 months, 35% of women were cured, 25% showed an improved pad weight result of 50% or better, and 40% failed therapy. The women that were cured or improved had a higher urethral closure pressure than those that failed (p less than 0.001). The authors note that a high pre-treatment urethral closure pressure may serve as a predictor for treatment success [54].

2) [IMIPRAMINE](#) 75 milligrams orally daily for four weeks was reported effective in the treatment of [female STRESS INCONTINENCE](#) in 21 of 30 women (71%). The drug was reported to extend the functional urethral length and make it independent of stress factors in women who

are continent after therapy. These data support that a shortened urethra can result in [urinary incontinence](#) and lengthening of the urethra by [IMIPRAMINE](#) treatment or vesicopexy will correct the dysfunction [55].

3j) [Bladder drill](#) is more effective than drug therapy in the treatment of incontinence due to idiopathic [detrusor instability](#) in women. Fifty women with [urinary incontinence](#) due to [DETRUSOR INSTABILITY](#) were randomly assigned to either in-patient [bladder drill](#) training or out-patient drug therapy ([FLAVOXATE HYDROCHLORIDE](#) 200 mg three times/day and [IMIPRAMINE](#) 25 milligrams three times/day) for 4 weeks [56]. At the completion of the study 84% (21/25) of the patients treated with [bladder drill](#) were continent and 76% were symptom free. Fifty-six percent (14/25) of the group treated with medication were continent and 48% were symptom-free. Side effects occurred in 56% of the patients receiving drug therapy and 5 patients discontinued drug therapy on their own secondary to side effects.

4j) Six of 10 elderly patients (x=80 year old, 63 to 88 years) with [urinary incontinence](#) associated with spontaneous unstable detrusor contractions were successfully treated with [IMIPRAMINE](#). The dose of [IMIPRAMINE](#) was started at 25 mg at bedtime and increased every third day by 25 mg, until the patient was continent, experienced side effects, or reached 150 mg/day. At the completion of the study 60% of the patients were continent. No correlation between dose or plasma concentrations of desmethyylimipramine and clinical or urodynamic effects could be found (Castleden et al, 1981).

d) Pediatric:

1j) Children and adolescents with [myelodysplasia](#) and incontinence (i.e. wet between their clean intermittent [catheterization](#) times performed 3 to 5 times daily) benefited from [imipramine](#) therapy. Children (n=19, 4- to 12-years-old) received [imipramine](#) 10 milligrams (mg) daily increased to a maximum of 20 mg twice daily. Combination therapy with [oxybutynin](#) was used in 10 patients. Eight of the children had also failed therapy with [oxybutynin](#), [flavoxate](#), or [ephedrine](#). With [imipramine](#), 15 children developed at least partial continence (dry 50% to 80% of the time) with 9 achieving complete continence (dry at least 80% of the time). The authors suggest low-dose [imipramine](#) alone or in combination with [oxybutynin](#) for children with [myelodysplasia](#) to help achieve continence [57].

#### 4.5.C] [Imipramine Pamoate](#)

##### 4.5.C.1] [Agoraphobia](#)

###### 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 the treatment of [agoraphobia](#) (Deltito et al, 1991)

Efficacy appears to be dose-related and usually requires doses of 150 milligrams or greater per day

###### c) Adult:

1) **Imipramine** and placebo were equally effective in the treatment of **agoraphobia** in a double-blind clinical trial combining drug therapy with brief psychological treatment [59]. The drugs were started 2 weeks prior to the initiation of the psychological therapy. At week 6 the mean dose of **IMIPRAMINE** was 124 milligrams and at week 14 it was 158 mg/day. During week 2 to week 12 each treatment group received 6 fortnightly sessions of therapist-aided relaxation. In addition each patient was given a leaflet describing the nature of **agoraphobia** and ways to cope with it. All patients were requested to complete systematic self-exposure homework and record these activities in a diary. Drug therapy was gradually withdrawn over weeks 26 to 28 of therapy. At the 2-year follow-up only 40 subjects were available. Five subjects had dropped out of the study (2 refused follow-up, 1 died, 1 moved out of the country, and 1 was untraceable). Two-thirds of the patients remained improved with regards to their phobias. There was no significant difference between those patients treated with **imipramine** or placebo therapy. Nor was there a superior effect of therapist-aided exposures over brief therapist-aided relaxation.

2) The plasma **IMIPRAMINE** levels, but not **DESIPRAMINE**, correlated with the improvement in **agoraphobia** [60], which may indicate that the antiphobic effects of **IMIPRAMINE** therapy are mediated through a post-synaptic serotonergic neurotransmitter system and not the noradrenergic system.

3) **IMIPRAMINE** therapy plus programmed in vivo exposure practice was superior to **IMIPRAMINE** therapy alone [61][62].

#### 4.5.C.2] **Anorexia nervosa**

##### a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

##### b) Summary:

Has resulted in some improvement in patients with **anorexia nervosa**

##### c) Adult:

1) **Imipramine** treatment resulted in some improvement in 7 patients with **anorexia nervosa** treated serially with several antidepressants (tricyclics, MAOIs, and triazolopyridines) including **imipramine**. Three of the patients received only **imipramine**; the treatment trials ranged from 6 to 14 weeks. Four of the patients had some improvement in anorexic symptoms, 2 experienced some weight gain, and 3 of 3 who had bulimic symptoms reported improvement. Improvement in anorexic symptoms (3 to 6 weeks) was slower than the improvement observed in depression and anxiety (2 to 4 weeks) following tricyclic therapy [77]. Significant weight gain generally began after 2 to 3 months. Patients treated with **IMIPRAMINE** tended to tolerate the drug poorly and appeared to have an extraordinary sensitivity to the drugs anticholinergic side effects when compared to patients treated with **trazodone** or MAOIs [77]. This extraordinary sensitivity to the drug's side effects may be associated with their low body weight.

**4.5.C.3] Bulimia nervosa****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:**

Approximately 75% of patients show at least a moderate response (reduction of binge eating by 50%) to antidepressant therapy

Monoamine oxidase inhibitors also appear effective in [bulimia](#), and may be superior to tricyclic antidepressants (Pope et al, 1983)

**c) Adult:**

1) Twenty bulimic subjects were followed for a period of up to 2 years to assess the long term efficacy of [IMIPRAMINE](#) therapy [64]. At the end of the follow-up period, 95% had at least partial improvement and 50% had experienced a complete remission. Over the course of the study period 85% had either maintained or improved upon the quality of their initial response. The one patient that failed to respond discontinued her medication and promptly relapsed to her original frequency of binge eating.

2) A retrospective study of 22 patients with [bulimia](#) treated with antidepressants ([AMITRIPTYLINE](#), [IMIPRAMINE](#), [DESIPRAMINE](#), [DOXEPIN](#), [TRAZODONE](#), [TRANALCYCLOPRIDINE](#), or [PHENELZINE](#)) showed a decreased incidence of bingeing and/or an improvement in depression [65]. During a 3-month follow-up period several patients relapsed despite continuation of their antidepressant therapy, while others continued to benefit from drug therapy.

**4.5.C.4] Cardiac dysrhythmia****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:**

Some patients with [ventricular tachycardia](#) or [premature ventricular contractions](#) may benefit from [imipramine](#) therapy

**c) Adult:**



1) **IMIPRAMINE** was included in a double-blinded crossover pilot study to evaluate the efficacy of **ventricular premature complex (VPC)** suppression after acute **myocardial infarction** as a means to improve survival [23]. Each patient was assigned to **ENCAINIDE**, **FLECAINIDE**, **IMIPRAMINE**, **MORICIZINE**, or placebo. The dose of the medication was adjusted to achieve 70% or greater reduction of **VPC** and greater than 90% reduction in unsustained **ventricular tachycardia**. If the patient failed to achieve an adequate response or was unable to tolerate the drug, the drug was discontinued and they were crossed over to a different antiarrhythmic class (class 1C to class 1A or class 1A to class 1C). **ENCAINIDE** (79%) and **FLECAINIDE** (83%) were superior to **IMIPRAMINE** (52%), **MORICIZINE** (66%), and placebo (37%) as first line-drugs. In patients failing **IMIPRAMINE** or **MORICIZINE** therapy, **ENCAINIDE** was 68% and **FLECAINIDE** 69% effective. It would appear that **IMIPRAMINE** is not the drug of choice for the prevention of **VPC** following an acute **myocardial infarction**. In addition, changes in therapy secondary to the development or worsening of **congestive heart failure** occurred in 26% of the treatment groups compared to 18% in the placebo group [80].

2) **IMIPRAMINE** in doses of 50 to 400 milligrams/day (mean = 210 +/- 103 mg/day) and **NORTRIPTYLINE** in doses of 75 to 150 mg/day (mean = 100 +/- 29 mg/day) were effective in the reduction of PVCs [81]. Seventy percent of the patients had a greater than 80% suppression of their PVCs. Neither drug significantly changed mean ejection fraction or peak systolic pressure end-systolic volume ratio. Both drugs produced a reduction in standing systolic blood pressure.

3) Twenty-two patients with 30 or more **ventricular premature complexes (PVCs)** per hour were treated with oral **IMIPRAMINE** 1 milligrams/kilogram/day (in two divided doses), increasing by 1 mg/kg/day every other day until PVCs were suppressed by at least 80% (or until adverse effects were observed or a daily dose of 5 mg/kg/day was administered). Eighteen patients (82%) exhibited antiarrhythmic effects from **IMIPRAMINE** therapy. All patients treated did not have psychological depression. The elimination half-life was approximately 8 hours, however, duration of action of the drug was much longer and antiarrhythmic effects were observed over at least a 12 hour period, which suggests that metabolites of **IMIPRAMINE** may contribute to the duration of antiarrhythmic efficacy [82].

4) In patients with **premature ventricular contractions**, **IMIPRAMINE** was noted to suppress **arrhythmias** by greater than 90% in 10 of 11 patients. **IMIPRAMINE** shortens action potential duration and decreases conduction velocity and maximal velocity and therefore is classified as a class 1 antiarrhythmic drug. Since the half-life of **IMIPRAMINE** is relatively long (12 to 18 hours) it may be dosed on a twice daily regimen. Antiarrhythmic doses appear to be similar to antidepressant doses (3.5 mg/kg/day). The antiarrhythmic activity of **IMIPRAMINE** is partially attributed to its metabolites, desmethyylimipramine and 2-hydroxyimipramine. Due to complications, **IMIPRAMINE** should not be used in patients with pre-existing conduction defects [83].

#### 4.5.C.5] Depression

##### FDA Labeled Indication

##### a) Overview

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive

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:**

Indicated for the relief of symptoms of depression [117]

[Endogenous depression](#) may be more likely to respond to [imipramine](#) therapy than other depressive states [117]

**c) Adult:**

1) Intramuscular S-adenosyl-L-methionine 1,4-butanedisulphonate (SAME) was found to be as efficacious as oral [imipramine](#) (IMI) for the treatment of depression. In a randomized, double-blind, comparative trial, patients with a diagnosis of [major depressive episode](#) according to DSM-IV criteria received SAME 400 milligrams (mg) by [intramuscular injection](#) once daily (n=146) or oral IMI 150 mg per day in 3 divided doses. Blinding was maintained by a double dummy model. The IMI dose was titrated over the first week to reach the full dose by day 8. Both treatments were given for 4 weeks. By all preestablished criteria (final score on the Hamilton Depression Rating Scale (HAMD), difference between baseline and final HAMD scores, percentage of responders defined as those with a Clinical Global Impression (CGI) endpoint score of 2 or less, and percentage of responders defined as those with a drop of at least 50% from baseline in HAMD scores), the 2 treatments were equivalent. By the CGI criterion, 68% of patients in the SAME group and 66% in the IMI group were responders; by the HAMD criterion, 59% of the SAME group and 50% of the IMI were responders. Drug related adverse reactions occurred in significantly fewer subjects of the SAME group than of the IMI group: 9.5% vs 33% (p=0.001). No relevant differences were observed in laboratory measures, vital signs, or ECG parameters [118].

2) Various depressive illnesses have responded to treatment with [IMIPRAMINE](#) in daily doses of 75 to 250 milligrams [2][3][4][5][6][7]; (Lindberg et al, 1979)[8]. Patients suffering from [endogenous depression](#) [7], non-endogenous depression (Lindberg et al, 1979), depression of [myotonic dystrophy](#) [9], [neurotic depression](#) [10] alcoholic patients with primary depression [11], and opiate-dependent patients with [depressive disorders](#) [12] may benefit from [IMIPRAMINE](#) therapy. However, the combination of [IMIPRAMINE](#) and a neuroleptic are effective in the treatment of delusional depression [13].

3) High dose tricyclic antidepressant therapy ([IMIPRAMINE](#) 150 to 200 milligrams/d, DESMETHYLIMIPRAMINE 150 to 500 mg/d) was effective in only a small portion of elderly patients with delusional depression. The dropout rate secondary to side effects was 58% and the overall success rate was only 25% [14].

**d) Pediatric:**

1) [IMIPRAMINE](#) is efficacious in the treatment of depression in children [15][16]. A general overview of the treatment of childhood behavioral and emotional disorders has been published [15].

2) Twenty-one children (ages 5.8 to 10.25 years) with various types of depression were treated with [IMIPRAMINE](#) WITH 67% of the children showing some improvement [18].

3) [Imipramine](#) was efficacious in the treatment of 20 prepubertal children hospitalized for [major depressive disorder](#) (DSM-III) with [imipramine](#) [19]. [IMIPRAMINE](#) therapy consisted of 75 milligrams/day, administered at bedtime, for the first 3 weeks and increased to a maximum of 5 milligrams/kilogram if no response. Serum [IMIPRAMINE](#) and [DESIPRAMINE](#) levels were

drawn during each phase of the study. During phase I, none of the 15 children with a total tricyclic antidepressant (TCA) plasma concentration outside the 125 to 225 ng/mL range showed a remission or improvement in their condition. Eighty percent of those children with serum levels between 125 to 225 ng/mL experienced a remission. During phase II, 12 of the 16 children achieved steady-state total TCA plasma concentrations of 125 to 225 ng/mL and 11 (92%) of them had experienced a remission by the end of the treatment period. Based on these results it can be concluded that **IMIPRAMINE** is effective in the treatment of depression in prepubertal children and its effectiveness is concentration-dependent.

#### 4.5.C.6] **Diabetic neuropathy**

##### a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

##### b) Summary:

Effective for **diabetic neuropathy** in selected patients

##### c) Adult:

1) In most patients, an **imipramine** plasma drug concentration of 400 to 500 nmol/L was sufficient to achieve maximal relief in the treatment of **diabetic neuropathy** [69]. All patients were diabetic and had one or more symptoms (pain, paresthesia, dysesthesia, and hypesthesia) and signs (reduction of sensibility, strength, or tendon reflexes) of **peripheral neuropathy**. One patient demonstrated no significant improvement even with **IMIPRAMINE** plus **DESIPRAMINE** levels below 400 nmol/L. In the other eleven patients doses of 125 to 350 milligrams/day were required to increase the levels to about 400 nmol/L. One patient required a blood level of 730 nmol/L to achieve maximal relief.

2) A double-blind, cross-over comparison of **IMIPRAMINE** with placebo was conducted in nine patients with symptomatic **peripheral diabetic neuropathy** [70]. The dose of **IMIPRAMINE** was adjusted to achieve a plasma **IMIPRAMINE** plus **DESIPRAMINE** level of 300 to 750 nmol (125 to 225 milligrams/day) during the first week. Each treatment period was three weeks and no washout phase was used between treatment periods. Efficacy was assessed at the end of each treatment period based on symptoms and measurement of peripheral and autonomic nerve function. **IMIPRAMINE** provided significant beneficial symptomatic improvement in all patients, but not beneficial changes in peripheral or autonomic nerve function.

3) **IMIPRAMINE** in doses of 50 milligrams (mg) daily for one week, then 100 mg daily for 4 weeks, was effective in producing improvement in 7 of 12 patients with severe **diabetic neuropathy** of the lower extremities in a double-blind, cross-over study [71]. **IMIPRAMINE** had beneficial effects on pain, paresthesia, dysesthesia numbness, and nocturnal aggravation.

#### 4.5.C.7] **Gardner-Diamond syndrome**

##### a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Effective only for short-term therapy of autoerythrocyte sensitization

**c) Adult:**

1) A 20-year-old female with autoerythrocyte sensitization and depression was treated with [IMIPRAMINE](#) therapy [78]. One week later the bleeding resolved and after 2 weeks the depression began to resolve. In 3 to 4 weeks all symptoms had resolved. Six weeks later, while still receiving therapeutic doses of [IMIPRAMINE](#), the depressive symptoms recurred and 10 days later bleeding restarted. Compared to previous episodes the severity of depression and bleeding was less severe. The bleeding resolved in 10 days and the depressive symptoms were gone within 6 weeks. Following a subsequent [relapse](#) in therapy the [IMIPRAMINE](#) was discontinued and [AMITRIPTYLINE](#) therapy (300 mg/d) was initiated. Since the start of [AMITRIPTYLINE](#) therapy the patient has been free of depression and bleeding for 10 months.

**4.5.C.8] Globus hystericus**

**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:**

Efficacy demonstrated in case reports only

**c) Adult:**

1) [Globus hystericus](#) syndrome is a condition in which the individual develops a fear that he/she is intermittently choking and unable to breathe. If the condition is left untreated the patient may become profoundly disabled or may develop a life-threatening weight loss. Case reports of three patients have shown that psychoactive drugs may be effective in controlling this condition. [IMIPRAMINE](#) therapy was effective in the treatment of one case, [PHENELZINE](#) in another, and [TRANLYCYPROMINE](#) in the other case [89]. Two additional cases of successful [imipramine](#) treatment of [globus hystericus](#) syndrome were reported [90][91].

**4.5.C.9] Obsessive-compulsive disorder**

**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:**

Questionable efficacy in the treatment of [obsessive-compulsive disorder](#)

**c) Adult:**

1) [Imipramine](#) was ineffective in treating [obsessive-compulsive disorder](#) (OCD) in a double-blind, placebo-controlled study that evaluated the efficacy of [IMIPRAMINE](#) in the treatment of depression and obsessive-compulsive symptoms in 37 patients [92]. Nineteen (10 women and 9 men) were treated with [IMIPRAMINE](#) and 18 (9 women and 9 men) were treated with a placebo. Each placebo patient received 10 tablets per day. The [IMIPRAMINE](#) group was started and increased by 25 mg every other day until clinical response, side effects, or a maximum daily dose of 250 mg. The average daily [IMIPRAMINE](#) dose was 233 mg (150 to 250 mg). At the end of 6 weeks the [IMIPRAMINE](#) was effective in reducing symptoms associated with depression, but had little to no effect on their obsessive-compulsive symptoms.

2) Four patients with obsessive-compulsive bowel obsessions were treated with [IMIPRAMINE](#) (3) or [DOXEPIN](#) (1). All 4 patients were free of their bowel obsession within 30 days (10, 14, 14, 30) of starting drug therapy (Jenike et al, 1987).

#### 4.5.C.10] Pain

**a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Pain has occasionally resolved with [imipramine](#) therapy

**c) Adult:**

1) Patients with chest pain, but normal [coronary angiograms](#), may respond to [imipramine](#) therapy [93]. The dose of medications used in the study were [imipramine](#) 50 milligrams at night and placebo in the morning, [clonidine](#) 0.1 milligrams twice daily, and placebo twice daily. The incidence of chest pain was decreased by 52 +/- 25% compared with 1 +/- 86% with placebo and 39 +/- 51% with [clonidine](#) therapy (data is presented as means +/- SD). Only pain relief associated with [imipramine](#) use was statistically significant (p=0.03). A follow-up evaluation of these patients, over an average of 21 months, indicated that none of the patients had been seen in an emergency room or had

been hospitalized because of chest pain. Seventeen patients have had the [imipramine](#) therapy discontinued and 16 asked to resume the [imipramine](#) therapy because of recurrent chest pain symptoms [94]. The mechanism of this pain relief is unknown, but may be a result of a visceral analgesic effect and not dependent on cardiac, esophageal, or psychiatric characteristics or gender. Another possible mechanism for this effect may be an increased pain threshold resulting from the reduction in psychological depression [95].

2)) A survey of Italian oncology centers revealed that 43% of their patients were given antidepressants. The most frequently utilized drugs were [AMITRIPTYLINE](#), [CLOMIPRAMINE](#), [IMIPRAMINE](#), and [TRAZODONE](#). Most physicians felt that the antidepressants were useful in controlling pain and were most efficacious in depressed patients [96].

3)) A case report of a 26-year-old graduate student being treated with [IMIPRAMINE](#) for suicidal thoughts and low self-esteem noted an improvement in her chronic pelvic pain (induced by [endometriosis](#) four years earlier) while on [IMIPRAMINE](#) therapy [97].

#### 4.5.C.11) [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:

Similar in efficacy to [alprazolam](#)

##### c)) Adult:

##### 1)) GENERAL INFORMATION

a)) The clinical response to [IMIPRAMINE](#) in the treatment of [panic disorder](#) is independent of the presence of depression or [dysphoria](#) [40]. Patients with high baseline depression scores have tended to have the poorest outcomes [41][42][43][44]. The use of [IMIPRAMINE](#) in the treatment of [panic disorder](#) may not be as safe as other anxiolytics in patients with [cardiovascular disease](#) [47].

2)) Combination [imipramine](#) and [cognitive-behavioral therapy](#) (CBT) was of limited value initially but provided advantages during maintenance therapy in patients with [panic disorder](#). Patients with [panic disorder](#) randomly received CBT alone (n=77), [imipramine](#) alone (n=83), placebo alone (n=24), CBT with [imipramine](#) (n=65), or CBT alone (n=63) for a 12- week acute treatment phase. Thereafter, responders entered a 6-month maintenance phase. Patient responses were evaluated following the 12- week acute treatment phase, the 6-month maintenance phase, and 6-months after therapy discontinuation; assessment tools included the [Panic Disorder Severity Scale](#) (PDSS) and the [Clinical Global Impression Scale](#) (CGI). Initial [imipramine](#) doses were 10 milligrams (mg)/day slowly increased over 5 weeks to 200 mg and further increased to 300 mg if symptoms continued. Following acute treatment, responses for the PDSS were 48.7% for CBT alone, 45.8%



for imipramine alone, 21.7% for placebo alone, 60.3% for CBT with imipramine, and 57.1% for CBT plus placebo. Both CBT alone and imipramine alone were significantly better than placebo ( $p=0.03$  and  $p=0.05$ , respectively), however, combination therapy provided no greater response rate over each treatment alone ( $p$  not significant). For the CGI during the acute phase, none of the therapies were significantly better than the others. Following maintenance therapy, responses on the PDSS were 39.5% for CBT alone, 37.8% for imipramine alone, 13% for placebo alone, 57.1% for CBT with imipramine, and 46.8% for CBT plus placebo. Responses on both the PDSS and the CGI were significantly better for imipramine versus placebo ( $p=0.02$  for both) and CBT versus placebo ( $p=0.02$ ,  $p=0.01$ , respectively). Using the PDSS, the combination therapy was significantly better than either CBT alone ( $p=0.04$ ) and better than imipramine alone ( $p=0.03$ ). On the CGI, combination therapy was only significantly better than imipramine alone ( $p=0.03$ ) and not better than CBT alone ( $p$  not significant). Following treatment discontinuation after the 6-month maintenance phase, the only statistical difference was the PDSS scores in the CBT group compared to the placebo group ( $p=0.05$ ) [48].

3) Maintenance treatment with imipramine had a significant protective effect against relapse in patients with panic disorder and agoraphobia. Patients who had shown an initial good and stable response to imipramine therapy over 24 weeks randomly received same-dose imipramine continuation ( $n=29$ ) or placebo discontinuation ( $n=27$ ). Patients continued their initial imipramine at a target dose of 2.25 milligrams/kilogram or discontinued their imipramine by decreasing the dose by 25% each week (substituted with placebo). During this study, no patient received behavioral or cognitive instructions unless a crisis-type intervention was needed. During the study, if relapse was confirmed the patient exited the study; relapse was defined as a worsening of their condition (measured as a 33% decline in the End- State Function scale score) accompanied by insistent requests for therapeutic action. After 12 months, the study population consisted of 20 patients in the imipramine group and 10 patients in the placebo group. This resulted in a 92.5% lower hazard rate of relapse with imipramine as compared to placebo [49].

4) In a double-blind study, an 8-month therapy period for panic disorder with either alprazolam or imipramine was effective [50]. Patients received alprazolam ( $n=37$ ), imipramine ( $n=34$ ), or placebo ( $n=35$ ) during an 8-week period of short-term treatment, a 6-month maintenance period, and then a 15-month follow-up period. Patients receiving alprazolam began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving imipramine began at 25 mg and were increased to 250 mg. Alprazolam patients had notable reductions in panic attacks during the first 2 weeks of therapy while imipramine patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates during this time were 11% in the alprazolam group, 41% in the imipramine group, and 57% in the placebo group ( $p$  less than 0.001 for alprazolam versus the other groups). In the remaining patients it was noted that tolerance developed to adverse effects during the maintenance phase. After the 6-month maintenance phase, doses were titrated off over 3 weeks. At this point, 62% of the alprazolam and 26% of the imipramine groups were panic-free ( $p$  less than 0.01). During the follow-up period, patients could be treated with non-study medications. Regardless of medication, patients who completed 8 months of treatment were more likely to be panic-free than those who had dropped out, even if they received non-study medications (85% versus 55%,  $p$  less than 0.01). Remission rates were higher in younger patients, those with a history of more frequent or intense panic attacks, those with a lower initial phobia score, and those with an initial lower score of inadequacy, low self-confidence, and passivity (Minnesota Multiphasic Personality Inventory Dependency Scale).

5) A comparison of cognitive therapy, applied relaxation, and imipramine found that at 3 months cognitive therapy was superior to both applied relaxation and imipramine therapy [51]. At 6

months the [cognitive therapy](#) and [imipramine](#) treatment produced similar results and were better than applied relaxation. However, between the 6th and 15th months of therapy, several of the [imipramine](#) patients relapsed while the patients treated with [cognitive therapy](#) continued to do better than with [imipramine](#) and relaxation therapy.

#### 4.5.C.12] [Posttraumatic stress disorder](#)

##### a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### b) Summary:

Resulted in improvement in positive symptoms of [post-traumatic stress disorder](#)

##### c) Adult:

1) [Imipramine](#) treatment resulted in improvement in positive symptoms of [post-traumatic stress disorder](#) (PTSD) in 10 patients [98]. Therapy was initiated at a low dose and increased over the following 7 days to the highest tolerable dose (mean 260 milligrams/day; range 50 to 350 mg/d). After 2 to 3 weeks of therapy, there was a significant decrease in the severity of forced recollection, sleep and dream disturbances, and a cessation or reduction in flashbacks. Most avoidance items, eg, staying away from reminders of the event, trying not to talk about the event, and trying to remove it from their memory, did not decrease significantly in severity. Based on these results it would appear that [IMIPRAMINE](#), in combination with psychotherapy, may be an effective treatment for patients.

2) Treatment of 3 patients with [acute post-traumatic stress disorder](#) (PTSD) with either [DOXEPIN](#) or [IMIPRAMINE](#) resulted in an improvement in PTSD symptoms [99]. Whether or not tricyclic antidepressant therapy is superior, equivalent, or inferior to psychotherapy or other means of treatment remains to be determined.

#### [4.5.C.13\] Separation anxiety disorder of childhood](#)

##### a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: [Pediatric, Class III](#)

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### b) Summary:

Routine use of tricyclic antidepressants is not recommended for separation anxiety in children

[Behavioral therapy](#) may be just as effective as [imipramine](#)

**c) Pediatric:**

**1)** The combination of [imipramine](#) and nonpharmacologic therapies (eg, parent management training, behavior therapy, and family therapy) may improve subjective comfort, reduce anxiety and somatic symptoms in 70% of the children experiencing separation-anxiety disorder [15]. This disorder is associated with a high rate of spontaneous recovery, therefore the routine use of tricyclic antidepressants is not recommended [15].

**2)** Both [IMIPRAMINE](#) and placebo therapy were equally effective for separation anxiety. A small, double-blind, randomized placebo-controlled study was conducted with 21 children with separation anxiety disorder [105]. All the children were first given a month of vigorous [behavioral treatment](#), then randomly assigned to [IMIPRAMINE](#) or placebo therapy for six weeks. Both treatments were approximately 50% effective.

**4.5.C.14] Sexual disorder**

**a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Effective in case reports only

**c) Adult:**

**1)** [IMIPRAMINE](#) may be useful, alone or in combination with [LITHIUM](#), in the treatment of men with [PARAPHILIAS](#) or NONPARAPHILIC SEXUAL ADDICTIONS [106]. Two patients with sexual disorders improved following [IMIPRAMINE](#) therapy. Whether [IMIPRAMINE](#) and other antidepressants are useful in the treatment of all males with [paraphilias](#) or nonparaphilic sexual addictions or just specific types remains to be determined.

**4.5.C.15] Sleep 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:**

Used successfully in the treatment of NIGHT TERRORS, SOMNABULISM, [NARCOLEPSY](#), and [CATAPLEXY](#)

**c) Adult:**

**1) [IMIPRAMINE](#)** therapy (50 to 100 milligrams at bedtime) resulted in a dramatic reduction in frequency and severity of night terrors in 2 patients unresponsive to [DIAZEPAM](#) therapy [107].

**2) [IMIPRAMINE](#)** therapy resulted in a significant reduction (242 +/- 156 to 142.8 +/- 120.1) in the total number of apneic episodes in 41.9% of the patients tested [108]. Based on these results it appears that [IMIPRAMINE](#) therapy may be an alternative form of therapy for some nonoverweight patients with negative ear, nose and throat (ENT) findings and for some patients who had not responded to weight reduction or ENT surgery.

**3) A 62-year-old female** had suppression of night terrors with [IMIPRAMINE](#) 50 milligrams at bedtime; 75 mg had completely suppressed night terrors but caused daytime drowsiness (Beitman & Carlin, 1979).

**4.5.C.16] Trichotillomania**

**a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: [Pediatric, Class IIb](#)

Strength of Evidence: Pediatric, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Used successfully in a case of [trichotillomania](#) and depression in a pediatric patient [110].

**4.6] Comparative Efficacy / Evaluation With Other Therapies**

**4.6.A] Adinazolam**

**4.6.A.1] Depression**

**a) SUMMARY:** In several small controlled studies, adinazolam has been as effective as [imipramine](#) in depressed patients, including patients with [melancholic depression](#).

**b) Several controlled studies** have reported the similar efficacy of adinazolam and [imipramine](#) in the treatment of [major depressive disorder](#) in outpatients [1094][1095]. Equivalent efficacy has also been observed in patients with more severe [melancholic depression](#) [1094]. However, all studies have employed only modest numbers of patients, lending themselves to a type II error. Larger studies of adequate duration, incorporating a placebo, are needed to adequately compare these two agents. In addition, compliance is always a problem in outpatient studies, especially involving depressed patients. Either a well-controlled inpatient study or the use of serum drug levels in future outpatient trials is required.

**c) Adinazolam and [imipramine](#)** had similar efficacy in the treatment of [major depressive disorder](#), with or without melancholic symptoms, in a double-blind study involving 43 outpatients [1094]. Following a 1-week, single-blind placebo period, patients were randomized to receive either adinazolam 10 milligrams (mg) three times daily initially, increasing up to 90 mg by day 14 of treatment if needed, or [imipramine](#)

25 mg three times day initially, increasing up to 225 mg by the second week of therapy, if required. Hamilton Depression Rating (HDR) scores and clinical global impression scale scores demonstrated the similar efficacy of both agents; there was trend toward lower HDR scores in the [imipramine](#) group at week 12 and more rapid improvement in the [adinazolam](#) group by week 1. Further analysis revealed the comparable efficacy of the 2 agents in patients with the more severe, melancholic, subtype of depression. Anticholinergic adverse effects of dry mouth, constipation, and blurred vision occurred more frequently in the [imipramine](#) group, as did lightheadedness, agitation and nervousness, whereas sedation or drowsiness was more prevalent in [adinazolam](#) patients. Mood swings into [hypomania](#) and worsening of depression were more frequent in the [adinazolam](#) group, with total episodes during study being 4 versus 1 and 3 versus 1, respectively. Other adverse effects occurred to a similar degree in each group.

#### 4.6.B] [Alprazolam](#)

##### 4.6.B.1] Anxiety

a) A six-week, double-blind, parallel study was conducted in 60 patients with [generalized anxiety disorder](#) to evaluate the efficacy of [alprazolam](#) and [imipramine](#) [1079]. After a three-week washout period, patients were equally divided and randomly assigned to [alprazolam](#) 0.5 milligram or [imipramine](#) 25 milligrams three times daily for six-weeks. After the first week the dose of the medication could be increased by one capsule daily up to a maximum of 12 capsules per day. At the end of the study the average dose was for the [alprazolam](#)-treated group was 2.2 mg/day (0.5 to 6 mg/day) and for the [imipramine](#) group 91 mg/day (25 to 200 mg/day). During the first two weeks, [alprazolam](#) was superior to [imipramine](#). After two weeks both drugs were effective based on psychic and somatic parameters, but [imipramine](#) predominantly affected psychic symptoms (eg, negative anticipatory thinking and [dysphoria](#)) as [alprazolam](#) was superior in attenuating somatic symptoms.

b) [Alprazolam](#) and [imipramine](#) might be useful in the treatment of school refusal ([school phobia](#)); however, further clinical trials need to be conducted to document their usefulness [1080].

##### 4.6.B.2] Depression

a) [Alprazolam](#) was as effective as [imipramine](#) in the treatment of primary depression [1061]. The mean effective doses of [alprazolam](#) in the study were 2.6 milligrams daily in divided doses, as compared with 128.4 milligrams daily for [imipramine](#). The onset of action with [alprazolam](#) was more rapid than that observed with [imipramine](#); antidepressant effects were more evident with [alprazolam](#) during the first week of therapy. A similar incidence of side effects occurred with each medication, with the main side effects being drowsiness, insomnia, nervousness, constipation and lightheadedness. However, [alprazolam](#) was reported to have less anticholinergic side effects (confusion, [tachycardia](#), palpitations, dry mouth, urinary retention). [Imipramine](#) was reported to cause fewer headaches than [alprazolam](#). However, a detailed description of side effects in these patients was not provided in this study. In addition, specific data regarding the onset of effects of each medication were also not provided satisfactorily. More importantly, the patient population ("primary" depression) is unclear in this study. It is difficult to evaluate which types of depression were being treated.

b) [Alprazolam](#) was compared with [imipramine](#) in a 6-week, double-blind study on 723 outpatients [1062]. Patients were selected with moderate to severe symptoms of a unipolar [major depressive disorder](#) of at least one month duration. Patients were given [imipramine](#) 25 milligrams two or three times daily or [alprazolam](#) 0.5 milligram two to three times daily initially, followed by increases in doses at one-week intervals to a maximum of 4.5 mg [alprazolam](#) and 225 mg [imipramine](#) daily. Both drugs were more effective than placebo in alleviating depression, with [alprazolam](#) being at least as effective as [imipramine](#). [Alprazolam](#) was reported more effective in relieving somatic symptoms and the data suggested an earlier onset of effect in some evaluated parameters, but the significance of this is questionable. Toxicity, primarily anticholinergic side effects, was reported in patients receiving [imipramine](#); drowsiness was the main side

effect reported with [alprazolam](#). This study suggests benefits of [alprazolam](#) in the treatment of [unipolar depression](#) as defined by the Feighner Diagnostic Criteria for primary depression (similar to the DMS-III Criteria for [major depression](#)). However, this study was performed on an outpatient basis, and even the best blinding techniques are useless if patients are taking other medications. The authors indicate that other psychotropic medications were not to be used except for "emergencies". Evaluation of drug response in depression is difficult at best, especially on an outpatient basis with several investigators doing the evaluation. [Alprazolam](#) may exhibit antidepressant effects.

**c)** [Alprazolam](#), [imipramine](#), and a placebo were compared in a 6-week, double-blind study of 175 patients with [major depressive disorder](#) (DSM-III) [1063]. Patients were randomly assigned to [alprazolam](#) (N=58), [imipramine](#) (N=60) or placebo (N=57) therapy. Dosage increases were allowed during the course of treatment and the mean dosage of [alprazolam](#) and [imipramine](#) during the last 2 weeks of treatment were 3 milligrams/day and 150 milligrams/day, respectively. Study results indicate that [alprazolam](#) was more effective than [imipramine](#) and placebo therapy. However it should be noted that a high placebo response rate was observed at 2 weeks (53% compared to 75% for [alprazolam](#) and 64% for [imipramine](#)). The high placebo response rate may be attributed to the fact that a high percentage of the patient were of the anxious and [agitated depression](#) subtypes. (Note: The data supplied in the figure comparing clinical improvement over time on the various forms of drug therapy is for 171 different patients, which is interesting since only 153 patients completed at least 4 weeks of treatment. No information is supplied regarding the study dropouts other than the fact that the dropout rates were not significantly different between the 3 treatment groups.) [Imipramine](#) therapy was associated with a higher incidence of drowsiness and dry mouth than [alprazolam](#) or placebo therapy.

**d)** The efficacy of [alprazolam](#) and [imipramine](#) were evaluated in the inpatient treatment of [depressive illness](#) [1064]. Patients were randomly assigned to either [alprazolam](#) or [imipramine](#) therapy. Dosage was individualized to patient response. Patients receiving [alprazolam](#) therapy improved over the first 10 days of therapy and then reached a plateau, whereas the patients treated with [imipramine](#) continued to improve in vegetative and cognitive symptomology. Further examination of the HAM-D scale indicated that the initial improvements seen with [alprazolam](#) is predominantly related to the vegetative features of the illness.

**e)** Both drugs administered once daily were efficacious in the treatment of outpatients with [major depressive disorders](#) [1065]. Fifty percent of the [alprazolam](#) treatment group had a greater than 50% improvement in their HAM-D scores, compared to the 38% success rate observed in the [imipramine](#) treatment group and 18% in the placebo treatment groups.

**f)** Patients who can be classified as DSM-III - [major depressive episode](#) but fail to satisfy more restrictive criteria for primary depression disorder appear to respond better to [alprazolam](#) therapy than [imipramine](#) therapy. Patients satisfying the stricter criteria for primary depression also appear to tolerate and respond better to [alprazolam](#) therapy initially. However, [imipramine](#) appeared to be more efficacious during long term therapy. In addition, patients with biologic depression (eg, melancholic, positive DST, and shortened REM latency) tended to respond better to [imipramine](#) therapy [1066].

**g)** An 8-week, double-blind, controlled study compared the efficacy of [alprazolam](#) (58 patients), [diazepam](#) (59 patients), [imipramine](#) (63 patients), and placebo (61 patients) in 241 outpatients with a DSM-III diagnosis of [major depression](#). Week 1 was a washout period with all patients receiving placebo. Week 2 through 7, the patients received their assigned medication, and during week 8 the dose of the medication was reduced by half for 3 days and discontinued for the remaining 4 days. At the end of the study the mean daily doses were 143 milligrams [imipramine](#), 3.1 milligrams [alprazolam](#), 24 milligrams [diazepam](#), and 6.8 capsules of placebo. Attrition rates were significant, 23% by week 4 of treatment and 39% by week 6. By the completion of the study, 41% of the [imipramine](#) group had withdrawn, 23% of the [alprazolam](#) group, 44% of the [diazepam](#) group, and 40% of the placebo group. The main reason given for attrition was side effects with the active compounds and ineffectiveness with placebo. [Alprazolam](#) and [imipramine](#) were both significantly better than placebo in treating depression, but [diazepam](#) was not effective. The clinical effects of [imipramine](#) and [alprazolam](#) were equivalent, and overall the frequency of side effects



was similar. Imipramine produced less drowsiness and more anticholinergic effects than both alprazolam and diazepam [1067].

#### 4.6.B.3] Panic disorder

a) Summary: Alprazolam and imipramine appear to be equally efficacious in the treatment of panic disorder in most patients. The onset of action is faster with alprazolam, but by the end of four weeks their effectiveness is similar (Rickels & Schweizer, 1998)[1068][1069][1070][1071][1072][1073][1074]. The decision to use imipramine over alprazolam should be based on patient-related characteristics (eg, concurrent depression, anxiety disorders, cardiovascular disease), potential drug interactions, and side effects.

b) In a double-blind study, an 8-month therapy period for panic disorder with either alprazolam or imipramine was effective (Rickels & Schweizer, 1998). Patients received alprazolam (n=37), imipramine (n=34), or placebo (n=35) during an 8-week period of short-term treatment, a 6-month maintenance period, and then a 15-month follow-up period. Patients receiving alprazolam began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving imipramine began at 25 mg and were increased to 250 mg. Alprazolam patients had notable reductions in panic attacks during the first 2 weeks of therapy while imipramine patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates during this time were 11% in the alprazolam group, 41% in the imipramine group, and 57% in the placebo group (p less than 0.001 for alprazolam versus the other groups). In the remaining patients it was noted that tolerance developed to adverse effects during the maintenance phase. After the 6-month maintenance phase, doses were titrated off over 3 weeks. At this point, 62% of the alprazolam and 26% of the imipramine groups were panic-free (p less than 0.01). During the follow-up period, patients could be treated with non-study medications. Regardless of medication, patients who completed 8 months of treatment were more likely to be panic-free than those who had dropped out, even if they received non-study medications (85% versus 55%, p less than 0.01). Remission rates were higher in younger patients, those with a history of more frequent or intense panic attacks, those with a lower initial phobia score, and those with an initial lower score of inadequacy, low self-confidence, and passivity (Minnesota Multiphasic Personality Inventory Dependency Scale).

c) Seventy-nine patients were enrolled in a placebo controlled, double-blind trial comparing the efficacy and cardiovascular effects of imipramine, alprazolam, and placebo in patients with panic disorders [1068]. Doses ranges were alprazolam 1 to 8 milligrams/day and imipramine 30 to 270 milligrams/day. In terms of global improvement, the patients treated with alprazolam or imipramine experienced significantly greater improvement than the placebo patients. Alprazolam had a more rapid onset of effect, but after four weeks of therapy no significant differences in efficacy were apparent between the alprazolam and imipramine treated patients. Imipramine did have a number of significant effects on the cardiovascular system, however, as the heart rate was significantly increased at resting and standing, and the systolic and diastolic blood pressures were raised.

d) Cerebrospinal fluid levels of homovanillic acid, 5-hydroxyindoleacetic acid, 3-methoxy-4-hydroxyphenylglycol, and somatostatin and beta-endorphin were measured in 12 patients with panic disorders who had been treated with alprazolam or imipramine for seven months. Seven patients treated with alprazolam (mean dose 4.7 mg, range 2 to 6 mg) all benefited from therapy. Four of the five imipramine-treated patients (mean dose 135 mg, range 100 to 150 mg) benefited. Cerebrospinal fluid levels of the monoamine metabolites and neuropeptides remained unchanged during therapy in both treatment groups, and were similar to levels measured in a control group, suggesting the antipanic activities of alprazolam and imipramine do not involve the monoamine or neuropeptide systems as was previously believed [1075].

e) A double-blind, placebo-controlled trial comparing the effects of imipramine and alprazolam in patients with panic disorders revealed both agents were significantly more effective than placebo, however the

patients treated with [alprazolam](#) reported less fear than the patients in the [imipramine](#) and placebo groups after eight weeks of therapy [1068].

**f)** The Cross-National Collaborative Panic Study compared [alprazolam](#), [imipramine](#), and placebo in the treatment of [panic disorder](#) [1071]. The study used in this evaluation was a double-blind, placebo-controlled, multicenter system enrolling 1168 patients with a diagnosis of [panic disorder](#) based on DSM-III criteria. Prior to the start of drug treatment all CNS active drugs were discontinued during a one- to two-week washout period. Patients were then randomly assigned to treatment with [alprazolam](#) 1 milligram, [imipramine](#) 25 milligrams, or placebo (1 tablet). The initial starting dose was increased steadily to 6 mg [alprazolam](#), 150 mg [imipramine](#), and 6 placebo tablets by day 19. Subsequently the dosage could be adjusted based on clinical response. Formal psychotherapy and [behavioral treatment](#) sessions were to be avoided during the eight week treatment phase. Efficacy was assessed by using global improvement scores, a panic attack scale, phobia scale, frequency of anticipatory anxiety, 14-item Hamilton Rating Scale for Anxiety, 21-item Hamilton Rating scale for Depression, and Hopkins SCL-90 patient self-rating scale. The treatment-cohort (anyone completing three weeks of therapy) consisted of 1010 patients and 812 patients completed the entire eight-week study. Reasons for dropping-out were side effects ([alprazolam](#) 3.4%, [imipramine](#) 5.9%, and placebo 3.1%), lack of efficacy ([alprazolam](#) 3.1%, [imipramine](#) 2.6%, and placebo 12.8%), treatment refusal (16.1%), and other reasons ([alprazolam](#) 7%, [imipramine](#) 7.7%, and placebo 11.8%); percentage are expressed as the number of patients affected divided by number of patients enrolled in that treatment group. Onset of therapeutic benefits was noted by week 1 and 2 with [alprazolam](#) and week 4 with [imipramine](#). By week 8 there was no difference between the [alprazolam](#) and [imipramine](#) groups and both groups were statistically superior to placebo.

**g)** [Alprazolam](#) was more effective than [imipramine](#) and placebo on anticipatory anxiety and phobic symptoms in a Scandinavian multicenter study in 41 patients with [panic disorder](#) [1076]. [Alprazolam](#) had a more rapid onset of action than [imipramine](#) on all symptoms. Patients receiving [alprazolam](#) had more drowsiness and those receiving [imipramine](#) had more anticholinergic effects.

**h)** In a study of 123 Scandinavian patients with [panic disorder](#), [alprazolam](#) had an early effect on variables relating to panic attacks, such as severity of spontaneous attacks and avoidance, whereas [imipramine](#) showed a more delayed effect on global measures [1077].

**i)** Patients with mild-to-moderate depression and [panic disorder](#) will respond equally to either [alprazolam](#) (avg dose = 5.25 milligrams/day) or [imipramine](#) (avg dose = 159 milligrams/day) therapy. Both drugs are more effective than placebo in the treatment of patients with mild-to-moderate depression and [panic disorder](#) [1078].

#### 4.6.C] Amineptine

##### 4.6.C.1] Depression

**a)** A controlled, double-blind study compared the efficacy and safety of amineptine (100 to 200 milligrams (mg) daily) with [imipramine](#) (50 to 100 mg/day) for two months in 33 patients who fulfilled the Diagnostic and Statistical Manual, third edition, (DSM-III) criteria for [major depressive disorders](#). Amineptine produced steady improvement of the symptoms of depression during treatment, according to the Hamilton ( $p = 0.001$ ) and Montgomery and Asberg ( $p = 0.002$ ) Depression Rating Scales and Clinical Global Impression Scale ( $p = 0.002$ ). [Imipramine](#) produced a significant improvement in the overall score and scale ( $p$  less than 0.001). No statistical differences were found between the two drugs; depressive symptoms improved from the 7th day of treatment for both amineptine and [imipramine](#). The incidence of anticholinergic adverse effects with amineptine was much lower than with [imipramine](#) [1252].

#### 4.6.D] Amisulpride

##### 4.6.D.1] [Dysthymia](#)

a) A double-blind, parallel group study compared the efficacy of amisulpride 50 milligrams (mg) daily versus [imipramine](#) 100 mg daily and placebo in the treatment of [dysthymia](#). No significant difference was found between the two drugs for efficacy, whereas amisulpride showed a tendency to generate fewer adverse effects [1275].

b) A double-blind study, six months in duration, compared the therapeutic effects of amisulpride (50 milligrams (mg) daily) to [imipramine](#) (200 mg daily) and placebo [1276]. The active drugs differed significantly from placebo according to the Clinical Global Impression scale (CGI), Montgomery and Asberg Depressive Rating Scale (MADRS), and Scale for the Assessment of Negative Symptoms (SANS) global score. Difference in efficacy between the active drugs was minimal.

#### 4.6.E] [Amitriptyline](#)

##### 4.6.E.1] Depression

a) Of 11 studies in which [amitriptyline](#) and [imipramine](#) were directly compared, 5 reported [amitriptyline](#) superior, 2 reported [imipramine](#) superior and 4 reported no difference between the 2 drugs in efficacy [1149][1150][1151][1152][1153][1154][1155].

b) In another study, [imipramine](#) (mean 157 milligrams/day) was compared with [amitriptyline](#) (mean 186 milligrams/day) in 25 post-psychotic depressed patients who were also receiving one of several neuroleptics (mean [chlorpromazine](#) equivalent 791 to 795 milligrams/day). Thirteen of 14 patients on [imipramine](#) improved, while 8 of 11 on [amitriptyline](#) improved [1156].

#### 4.6.F] [Amoxapine](#)

##### 4.6.F.1] Depression

a) SUMMARY: Clinical studies have demonstrated that [amoxapine](#) is at least as effective as [imipramine](#) in the treatment of depression [1103][1104][1105][1106][1107][1108][1109][1110][1111][1112]. Side effects of the drug are comparable in type, frequency, and intensity to [imipramine](#) [1113][1114].

b) [Maprotiline](#) (mean, 165 mg daily) and [amoxapine](#) (mean, 230 mg daily) showed similar efficacy in the treatment of moderate-to-severe depression in a 4-week, double-blind study involving 76 outpatients. [Amoxapine](#) is reported to have a more rapid onset of action than [maprotiline](#) as evidenced by a greater improvement at days 4 and 7 [1115].

c) Equivalent doses of [amoxapine](#) and [imipramine](#) were equally effective in depressed outpatients during 5- to 6-week, double-blind clinical trials [1112][1104]. [Amoxapine](#) produced improvement in a 6-week, double-blind study involving 90 depressed outpatients more rapidly than did [imipramine](#); however, the dose of [amoxapine](#) (210 milligrams/day) was double that of [imipramine](#) (105 milligrams/day) [1108].

d) [Imipramine](#) and [amoxapine](#) were comparable in the treatment of depression in inpatients in a controlled study. [Amoxapine](#) in mean doses of 165 milligrams daily was reported comparable with [imipramine](#) 175 milligrams daily in management of [depressive illness](#); however, the imipramine-treated patients had slightly more cardiovascular side effects. Amoxapine-treated patients reportedly had slightly more neurological toxicity [1116].

e) [Amoxapine](#) and [imipramine](#) were comparable in 90 adult outpatients with mixed depressive illnesses in a 6-week, placebo-controlled, double-blind study. Patients received [amoxapine](#) 145 to 265 milligrams daily (mean 235 mg) or [imipramine](#) 75 to 150 milligrams daily (mean 122.5 mg). [Amoxapine](#) and [imipramine](#) were both significantly superior to placebo as demonstrated by the Hamilton Rating Scale for depression, Zung Self- Rating Scale, and Clinical Global Impression Scale scores. However, there were no significant differences between the 2 drugs [1106].

##### 4.6.F.2] Efficacy

a) Continuous Performance Test (CPT), a visual vigilance test, of [amoxapine](#) and [imipramine](#) show several differences in performance and brain function [1117]. [Amoxapine](#) enhanced N120 amplitude in midline parietal and right parietal cortex. Both [amoxapine](#) and [imipramine](#) enhanced the P200 area, with [amoxapine's](#) greatest effect being seen over midline parietal locations. The clinical importance of these differences in brain activity remains to be determined.

#### 4.6.G] Binedaline

##### 4.6.G.1] Depression

a) Binedaline, a bicyclic antidepressant, was evaluated against [imipramine](#) therapy in the treatment of 50 hospitalized endogenously depressed patients [1176]. Patients were either treated with 150 mg/d of [imipramine](#) or 300 mg/d of binedaline in 3 equally divided doses. There was no psychiatric, clinical or statistical differences between the 2 treatment groups. Binedaline efficacy was slightly higher than [imipramine](#) utilizing the clinical global impression scale. Frequency of side effects was less in the binedaline treatment group.

#### 4.6.H] Brofaromine

##### 4.6.H.1] Depression

a) Brofaromine is a selective and reversible monoamine oxidase inhibitor (MAOI). In addition, the drug may be a 5-HT-reuptake inhibitor. A comparison of brofaromine with [imipramine](#) was made in 216 outpatients with depression. Patients were randomly assigned to brofaromine and [imipramine](#) therapy in a 2:1 ratio. Both medications were started at a daily dose of 25 to 50 milligrams. The average dose of medication at the end of eight weeks was brofaromine 93.1 mg/day and [imipramine](#) 92 mg/day. This phase of the study lasted eight weeks. Baseline HAMD scores were 29.4 in the brofaromine group and 28.2 in the [imipramine](#) group. At the end of the study period the HAMD scores were 9.34 and 12.31 ( $p=0.01$ ), respectively. The frequency of adverse reactions was 27.8% in the brofaromine group (eg, headache, sleep disturbances, palpitation, nausea) and 40.3% in the [imipramine](#) group (eg, dryness of mouth accommodation disturbances, impaired vision, and sweating). During the next two phases of the study only those patients receiving brofaromine were followed for up to 52 weeks. The lower HAMD scores continued to be maintained, with the exception of a slight increase between weeks 28 to 36, and the drug was well tolerated [1174].

#### 4.6.I] Bromocriptine

##### 4.6.I.1] Depression

a) No significant differences were observed in 33 outpatients with [endogenous depression](#) treated with either [bromocriptine](#) or [imipramine](#). Sixteen patients received [bromocriptine](#) 10 to 60 milligrams (mg)/day (mean, 34 mg/day) and seventeen patients received [imipramine](#) 75 to 250 mg/day (mean, 143 mg/day) for a period of 6 weeks. Based on the Hamilton rating scale, the total score of the bromocriptine-treated patients decreased from 19.9 to 7.8 and the imipramine-treated patients decreased from 20.1 to 6.1. Side effects associated with [bromocriptine](#) included nausea, dizziness and headache and those seen with [imipramine](#) included dryness of mouth, dizziness, and sweating. Although [bromocriptine](#) has an antidepressant effect, its effects on anxiety, agitation, and insomnia are less pronounced than that of [imipramine](#) [1097].

b) [Bromocriptine](#) (15 milligrams (mg) daily) was as effective as [imipramine](#) (75 mg/day daily) in a 10-week, double-blind study in patients with [endogenous depression](#). However, only 9 patients were evaluated and more studies are necessary to determine definite effects of the drug [1098].

#### 4.6.J] Bupropion

##### 4.6.J.1] Depression

a) A meta-analysis of published studies between 1980 and 1990 comparing **imipramine** and **bupropion** in the treatment of **major depression** indicates that both medications are equally effective [1190].

b) **Bupropion** and **imipramine** were equally efficacious in a double-blind, 5-week, multicenter trial in 63 elderly depressed patients [1191]. Patients were given either **bupropion** 150 milligrams/day (18 patients), **bupropion** 300 to 450 milligrams/day (18 patients), **imipramine** 150 milligrams/day or less (18 patients), or placebo (9 patients). Assessment of treatment efficacy utilized depression and anxiety scales. All 3 drug treatment groups were more effective than placebo by day 7 to 35.

##### 4.6.J.2) Adverse Effects

a) **Bupropion** may be safer than **imipramine** in treating depressed patients with **congestive heart failure** [1192]. The cardiovascular effects of **imipramine** and **bupropion** were compared in 10 depressed patients with **congestive heart failure**. Neither drug had an effect on left ventricular ejection fraction or left ventricular function. Hypotension, severe enough to require discontinuation, was a problem in 50% of the **imipramine** patients but did not occur with **bupropion**.

#### 4.6.K] Buspirone

##### 4.6.K.1] Depression

a) **Imipramine** was more effective than placebo (p less than 0.01) while **buspirone** trended towards being more effective than placebo (p less than 0.1) for the treatment of **major depression** in elderly outpatients. The 8-week, randomized, double-blind, placebo-controlled study involved 177 patients aged 65 years and over. Beginning dosages were **imipramine** 25 milligrams (mg) twice daily or **buspirone** 10 mg twice daily, increased to **imipramine** 25 mg three times daily and **buspirone** 10 mg three times daily after one week. If tolerated after the second week, **imipramine** was increased to 100 mg/day and **buspirone** to 40 mg/day in divided doses. A daily maximum dose of 150 mg of **imipramine** and 60 mg of **buspirone** could be reached based on clinical response, with the mean optimal dose of 89 mg/day for **imipramine** and 38 mg/day for **buspirone**. Following 8 weeks of treatment, moderate to marked global improvement occurred in 61% of **buspirone** patients, 70% of **imipramine** patients, and 42% of placebo patients [1167].

##### 4.6.K.2] Panic disorder

a) A placebo-controlled, double-blind study of outpatients with **panic disorder** or **agoraphobia with panic attacks** failed to show any significant differences in total biweekly numbers of panic attacks, decreases in number of attacks, and evaluations of psychopathology and of global improvement over an eight-week period between patients treated with **buspirone**, **imipramine**, or placebo. All groups improved. The inconclusive results may have been due to a number of factors, including small sample sizes, the episodic nature of the illness, a possible therapeutic effect of the diagnosis for the subjects (many of whom were diagnosed for the first time during the study), and the limited study duration [1165]. Somewhat better results were seen for both active treatments in a study using higher doses [1166].

#### 4.6.L] Butylscopolamine

##### 4.6.L.1] Nocturnal enuresis

a) **Imipramine** was significantly superior to butylscopolamine, which was no better than placebo in 14 children with nocturnal **enuresis** [1164]. **Imipramine** 10 or 20 milligrams was compared to butylscopolamine 10 or 20 milligrams. The investigators concluded that antimuscarinic activity is not

sufficient to inhibit detrusor contraction and that oral butylscopolamine is not absorbed to any significant extent.

#### 4.6.M] **Chlordiazepoxide**

##### 4.6.M.1] **Depression**

a) **Imipramine** was more effective and better tolerated at assessments made at 4 weeks, 6 weeks, and 8 weeks in 387 patients with primary depression who completed a double-blind comparison of **imipramine**, **chlordiazepoxide**, and placebo [1247]. At the end of 2 weeks of therapy the therapeutic advantages associated with **imipramine** therapy were becoming apparent. By weeks 6 and 8, the **imipramine**-treated group had a marked superior therapeutic advantage in improving the symptoms of depression, anxiety, anger-hostility, interpersonal sensitivity, and global improvement. **Chlordiazepoxide** offered an advantage in patients with sleep difficulties, but these patients did significantly worse on anger-hostility and interpersonal sensitivity.

#### 4.6.N] **Chlorprothixene**

##### 4.6.N.1] **Depression**

a) **Imipramine** 75 to 225 milligrams/day and **chlorprothixene** 45 to 135 milligrams/day had comparable efficacy in a 6-week double-blind, randomized, crossover study involving 32 patients with **depressive disorders**. The investigators concluded that both drugs were equally efficacious and safe, although the side effect profiles varied [1168].

#### 4.6.O] **Citalopram**

##### 4.6.O.1] **Depression**

a) Unpublished studies involving small numbers of patients suggest the comparable efficacy of **imipramine** and **citalopram** in depression, although **imipramine** has tended to be more effective in improving sleep disturbances [1169]. Further well-controlled comparisons of these agents are needed.

#### 4.6.P] **Clomipramine**

##### 4.6.P.1] **Depression**

a) **Clomipramine** was as effective as **imipramine** in treating depression in 24 patients during a 44-day, randomized, double-blind study [1170]. 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.P.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** [1171]. 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 [1172]. 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 [1173]. 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 [1172].

#### 4.6.Q] [Clonazepam](#)

##### 4.6.Q.1] [Panic disorder](#)

a) Preliminary results from an ongoing double blind study comparing [imipramine](#) and [clonazepam](#) in the treatment of [panic disorders](#) in twelve patients have been reported [1193]. Six patients received [imipramine](#) and six received [clonazepam](#), and all were treated for a total of six months. [Clonazepam](#) treated patients required an average of 1.6 mg/day (range 1 to 3 mg/day) to achieve relief of symptoms; [imipramine](#) patients required 62.5 mg/day (range 25 to 75 mg/day). During the final four months of the study no patients required more than 2 mg/day of [clonazepam](#) or 50 mg/day of [imipramine](#). Over the course of the first two weeks of treatment a substantial drop in the incidence of panic attacks occurred in both groups. Mean scores in global improvement were significantly improved in both groups, as were patients assessed scores and physician assessed scores. These early results demonstrate the efficacy of both [imipramine](#) and [clonazepam](#) in the control of [panic disorders](#).

#### 4.6.R] [Delorazepam](#)

##### 4.6.R.1] [Anxiety](#)

a) Delorazepam 3 to 6 milligrams (mg) was compared to [imipramine](#) 50 to 100 mg/day and [paroxetine](#) 20 mg/day for at least 8 weeks in 81 patients with [generalized anxiety disorders](#) according to DSM-IV criteria. Delorazepam produced the greatest improvement in anxiety ratings during the first two weeks of treatment, but both [paroxetine](#) and [imipramine](#) were more effective by the fourth week of treatment. At study end, reduction of at least 50% in the Hamilton Rating Scale for Anxiety score was reported in 55% of the delorazepam patients, compared with 68% and 72% for [paroxetine](#) and [imipramine](#), respectively.

Delorazepam affects predominantly somatic symptoms, whereas [paroxetine](#) and [imipramine](#) affect psychic symptoms [1157].

#### 4.6.S] [Desipramine](#)

##### 4.6.S.1] Depression

a) [Desipramine](#) has been evaluated in comparison with [imipramine](#) with most open or double-blind trials indicating that both drugs are equally effective with similar time of onset and side effects and that no significant differences or advantages are apparent with either drug [1284][1285][1286][1287][1288][1289]. However, other limited data indicates that [imipramine](#) may be superior in terms of being more active [1290][1291] or, conversely, that [desipramine](#) has the advantage of fewer side effects and earlier clinical response [1292].

#### 4.6.T] [Desmopressin](#)

##### 4.6.T.1] Nocturnal [enuresis](#)

a) Patients treated with oral [imipramine](#) followed by intranasal [desmopressin](#) therapy (n=28) experienced additive effects compared to those who received [desmopressin](#) followed by [imipramine](#) (n=29) in an open label, cross-over study in patients with nocturnal [enuresis](#) [1085]. Following a 2 week observation period, patients were randomized to receive either [desmopressin](#) 30 micrograms per day (mcg/day) (3 puffs per nostril) for 3 weeks followed by oral [imipramine](#) 0.9 milligrams per kilogram (mg/kg) for 3 weeks followed by 2 more weeks of follow up, or [imipramine](#) therapy first followed by [desmopressin](#). Both patient groups experienced significant reductions in the number of wet nights in the first 3 weeks of therapy compared to the first observation period (p value not specified). Irrespective of which agent was administered first, [desmopressin](#) therapy significantly increased the number of dry nights per week compared to [imipramine](#) (p less than 0.0001). Overall, [desmopressin](#) was associated with 20% wet nights while [imipramine](#) was associated with 37% wet nights. During follow up, patient who received [desmopressin](#) last had fewer weekly wet nights than those who received [imipramine](#) last. The authors suggest the results of this study indicate [desmopressin](#) is long acting and is safe for long-term treatment of nocturnal [enuresis](#). Both agents were well tolerated with few adverse events reported. One [imipramine](#) patient experienced pallor, restlessness, and cold extremities. One [desmopressin](#) patient reported inflammation of nasal mucosal.

#### 4.6.U] [Diazepam](#)

##### 4.6.U.1] Depression

a) An 8-week, double-blind, controlled study compared the efficacy of [alprazolam](#) (58 patients), [diazepam](#) (59 patients), [imipramine](#) (63 patients), and placebo (61 patients) in 241 outpatients with a DSM-III diagnosis of [major depression](#). Week 1 was a washout period with all patients receiving placebo. Week 2 through 7, the patients received their assigned medication, and during week 8 the dose of the medication was reduced by half for 3 days and discontinued for the remaining 4 days. At the end of the study the mean daily doses were 143 mg [imipramine](#), 3.1 mg [alprazolam](#), 24 mg [diazepam](#), and 6.8 capsules of placebo. Attrition rates were significant, 23% by week 4 of treatment and 39% by week 6. By the completion of the study, 41% of the [imipramine](#) group had withdrawn, 23% of the [alprazolam](#) group, 44% of the [diazepam](#) group, and 40% of the placebo group. The main reason given for attrition was side effects with the active compounds and ineffectiveness with placebo. [Alprazolam](#) and [imipramine](#) were both significantly better than placebo in treating depression, but [diazepam](#) was not effective. The clinical effects of [imipramine](#) and [alprazolam](#) were equivalent, and overall the frequency of side effects was similar. [Imipramine](#) produced less drowsiness and more anticholinergic effects than both [alprazolam](#) and [diazepam](#) [1175].

#### 4.6.V] Dibenzepin

##### 4.6.V.1] Depression

a) Dibenzepin and [imipramine](#) are both well tolerated and equally effective in the treatment of depression. In this double-blind comparative trial, depressed patients (n=22) were administered either dibenzepin (160 milligrams (mg) three times daily) or [imipramine](#) (50 mg three times daily) for 4 weeks. Both drugs were effective and no significant differences were found between patients taking dibenzepin and those taking [imipramine](#) [1177].

#### 4.6.W] [Diclofenac](#)

##### 4.6.W.1] [Cancer](#) pain

a) In a 1-week study, [diclofenac](#) plus placebo was as effective as [diclofenac](#) plus [imipramine](#) or [diclofenac](#) plus [codeine](#) for [cancer](#) pain. This double-blind study enrolled 180 patients who were randomly assigned to receive [diclofenac](#) 50 milligrams (mg) 4 times daily with placebo, [diclofenac](#) with [imipramine](#) 10 or 25 mg 3 times daily (determined by patient age less than or greater than 65 years), or [diclofenac](#) with [codeine](#) 40 mg 4 times daily. Efficacy was assessed at baseline and at 4 days with a 100 millimeter(mm) visual analogue scale (VAS) (0=no pain; 100=worst possible pain); patients with acceptable pain control continued treatment for the remainder of the study. Significant differences were NOT detected between the 3 treatments. Results of this study are limited by the short duration of treatment which may have been insufficient to detect beneficial effects of [imipramine](#), lack of dose titration for [codeine](#), concomitant use of [morphine](#) in 30 patients, and inclusion of patients with different [cancer](#) pain etiologies. Additional studies which address the limitations of this study are needed [1083].

##### 4.6.W.2] Depression

a) Diclofensine is a isoquinoline derivative, structurally similar to nomifensine, that is a potent inhibitor of 5-hydroxytryptamine, [dopamine](#), and [norepinephrine](#) reuptake [1084]. In a double-blind comparison with [imipramine](#), low (average dose = 65 milligrams/day) and high dose (average dose = 97.6 milligrams/day) diclofensine therapy was shown to be as effective as [imipramine](#) therapy (average dose = 102.9 milligrams/day) during the 6-week study period. During the first few weeks of therapy diclofensine therapy was more effective, but by the completion of the 6-week study period there was no difference between the treatment groups. Whether or not a difference in onset of action would have been observed if higher initial doses of [imipramine](#) were used is unknown. Diclofensine therapy was better tolerated than the [imipramine](#) therapy, thus even if higher doses of [imipramine](#) were used it would have resulted in an even higher incidence of side effects.

#### 4.6.X] Dothiepin

##### 4.6.X.1] Depression

a) Dothiepin and [imipramine](#) appear to be equally efficacious in the treatment of depression. In a double-blind study, 36 patients with existing depression received either dothiepin or [imipramine](#). Therapy was initiated with 25 milligrams 3 times daily, which was increased to a maximum of 250 milligrams/day based on clinical response. Although both dothiepin and [imipramine](#) groups showed similar improvement, dothiepin was associated with fewer adverse effects, including dry mouth and limb tremor [1081]. Similar results were seen in another study [1082].

#### 4.6.Y] [Doxepin](#)

**4.6.Y.1] Depression**

a) **Imipramine** may be slightly more effective than **doxepin** in the treatment of depression. Ninety-nine patients with **neurotic depression** received **imipramine** 100 to 200 milligrams/day or **doxepin** 100 to 200 milligrams/day for 4 weeks in a double-blind study. **Imipramine** was superior in 24 of 27 parameters. **Imipramine** was shown to be superior to **doxepin** in improving the symptoms of anxiety/depression; global evaluations showed improvement in 39 of 48 (81%) of **imipramine** patients and 34 and 49 (69%) of **doxepin** patients [1088].

b) In a study involving 79 patients, a higher socioeconomic status and shorter duration of illness were indicative of a favorable response to **imipramine**, whereas a higher response rate to **doxepin** was found in male patients [1089].

c) **Amitriptyline** was superior to **imipramine** and **doxepin** in relation to their effects on interpersonal learning in 50 depressed inpatients [1090]. All subjects performed better, according to quantitative indices of learning tasks, than patients who received antipsychotic or neuroleptic drugs but no antidepressants. **Amitriptyline** patients scored significantly higher than either **imipramine** or **doxepin** patients.

d) No significant differences in overall efficacy of the 2 drugs was reported in one study [1091], but **doxepin** 30 to 150 mg daily was superior to **imipramine** 150 mg daily in **neurotic depression**, whereas **imipramine** appeared to be superior to **doxepin** in **endogenous depression** [1092].

e) Similar antidepressant effects of **doxepin** and **imipramine** were reported; however, **imipramine** had a more rapid onset of action. **Doxepin** appeared to have more sustained effects [1093].

**4.6.Y.2] Efficacy**

a) In elderly patients **doxepin** produces less orthostatic effects than **imipramine** (10.5 mmHg vs 25.9 mmHg). The orthostatic effect observed with **imipramine** was weakly related to dose and did not correlate with pretreatment orthostatic hypotension or with duration of treatment [1087].

**4.6.Z] Electroconvulsive therapy****4.6.Z.1] Depression**

a) A double-blind, randomized, controlled trial compared **electroconvulsive therapy** (ECT) with **imipramine** therapy in 32 patients suffering from depression [1086]. Group I received modified bilateral ECT using thiopentone 150 to 250 mg, **succinylcholine** 20 to 30 mg, and **atropine** 0.65 mg during the procedure. ECT was administered every other day during the first 2 weeks for a total of 6 treatments and then once a week for the next 2 weeks. Following this period, 3 maintenance ECTs were administered in the next 8 weeks. During the course of this treatment the patients received capsules identical to the **imipramine** group. Group II received **imipramine** 75 milligrams/day during week one and 150 mg/day during the second through the eleventh week. The dose was reduced to 75 mg/day during the twelfth week. During the course of therapy each patient received a simulated course of **ECT therapy** at the same frequency as the ECT-treated group. Twenty-four patients completed the study period (5 patients in the ECT group and 3 patients in the **imipramine** group were excluded from the study during the first 6 weeks). Both treatments produced equally significant improvement which was maintained during the 6-month follow-up period. The rate of improvement was quicker in those patients receiving **ECT therapy**. **ECT therapy** produced fewer side effects than **imipramine** therapy. There was no lasting organic **brain dysfunction** associated with the **ECT therapy**, as previously thought.

**4.6.AA] Encainide****4.6.AA.1] Cardiac dysrhythmia - Myocardial infarction with complication, Post**

a) **Encainide** and **flecainide** were more effective in suppressing **ventricular arrhythmias** than **morizine**, **imipramine**, and placebo during the dose titration phase of a 1-year, multicenter, randomized, double-blind, placebo-controlled study of 502 patients [1232]. Patients were eligible for this study if they had an acute **myocardial infarction** within 6 to 60 days of entrance to the study, were less than 75 years of age and demonstrated either an average of 10 or more **ventricular premature complexes** (VPCs) per hour, or 5 or more episodes of unsustained **ventricular tachycardia** during a 24-hour **ambulatory ECG** recording. The total daily doses of the study drugs were **encainide** 105 to 180 milligrams, **flecainide** 200 to 400 mg, **imipramine** 150 to 375 milligrams, and **morizine** 600 to 900 mg. Efficacy was defined as 70% or more suppression in **VPC** frequency and more than 90% suppression of runs of **VPC** when compared with baseline. The efficacy rates were 83% for **flecainide**, 79% for **encainide**, 66% for **morizine**, 52% for **imipramine**, and 37% for placebo during the dose titration phase of the study. The incidence of adverse effects was 49% for **encainide**, 55% for **flecainide**, 67% for **imipramine**, 64% for **morizine**, and 60% for placebo. **Imipramine** was the drug most associated with patient withdrawal due to adverse effects. This study did not address **VPC** suppression efficacy at the 1-year follow-up.

#### 4.6.AB] **Flecainide**

##### 4.6.AB.1] **Cardiac dysrhythmia - Myocardial infarction with complication, Post**

a) **Encainide** and **flecainide** were more effective in suppressing **ventricular arrhythmias** than **morizine**, **imipramine**, and placebo during the dose titration phase of a 1-year, multicenter, randomized, double-blind, placebo-controlled study of 502 patients [1102]. Patients were eligible for this study if they had an acute **myocardial infarction** within 6 to 60 days of entrance to the study, were less than 75 years of age and demonstrated either an average of 10 or more **ventricular premature complexes** (VPCs) per hour, or 5 or more episodes of unsustained **ventricular tachycardia** during a 24-hour **ambulatory ECG** recording. The total daily doses of the study drugs were **encainide** 105 to 180 milligrams, **flecainide** 200 to 400 mg, **imipramine** 150 to 375 milligrams, and **morizine** 600 to 900 mg. Efficacy was defined as 70% or more suppression in **VPC** frequency and more than 90% suppression of runs of **VPC** when compared with baseline. The efficacy rates were 83% for **flecainide**, 79% for **encainide**, 66% for **morizine**, 52% for **imipramine**, and 37% for placebo during the dose titration phase of the study. The incidence of adverse effects was 49% for **encainide**, 55% for **flecainide**, 67% for **imipramine**, 64% for **morizine**, and 60% for placebo. **Imipramine** was the drug most associated with patient withdrawal due to adverse effects. This study did not address **VPC** suppression efficacy at the 1-year follow-up.

#### 4.6.AC] **Fluoxetine**

##### 4.6.AC.1] **Depression**

a) SUMMARY: **Fluoxetine** has been as effective as **imipramine** in the treatment of depression, while producing a lower incidence of side effects. Overall cost of therapy, clinical efficacy, and patient quality of life have been shown to be equivalent after six months of treatment.

b) In a double-blind, randomized, parallel group study, **fluoxetine** was better tolerated although not more effective than **imipramine** in the treatment of **major depression** with atypical features. A total of 154 patients (age 18 to 65 years) who met DSM-IV criteria for **major depression** for at least 1 month and also met the Columbia criteria for **atypical depression** were randomized to receive **fluoxetine**, **imipramine**, or placebo for 10 weeks. **Fluoxetine** was administered as 20 milligrams (mg) daily for 4 weeks, 40 mg daily for week 5, and 60 mg daily for the remaining weeks. **Imipramine** was administered as 50 mg daily for the first week, increasing by 50 mg/day each week until a maximum of 300 mg daily was reached. Mean daily doses at the end of the study were 51.4 mg/day for **fluoxetine** and 204.9 mg/day for **imipramine**. **Fluoxetine** and **imipramine** did not differ from one another based on the Clinical Global Impression (CGI) scale improvement scores following 10 weeks of treatment. **Fluoxetine** and **imipramine** were significantly



more effective than placebo in the intention-to-treat ( $p$  less than 0.007 and 0.003, respectively) and completer groups ( $p$  less than 0.03 and 0.001, respectively). Imipramine-treated patients demonstrated a significantly higher dropout rate than fluoxetine-treated patients ( $p=0.04$ ). In the intention-to-treat group, depression outcome measures including the 17-item and 28-item Hamilton Depression Rating Scale and Patient Global Improvement demonstrated no differences between fluoxetine and imipramine and a consistent clinical benefit of both treatment groups compared with placebo. Adverse effects significantly more common for imipramine than for fluoxetine included dry mouth (81% versus 28%, respectively), somnolence (42% versus 24%, respectively), and dizziness (44% versus 25%, respectively); cough and back pain occurred at a significantly higher incidence in fluoxetine- versus imipramine-treated patients [1118].

c) For the initial treatment of depression, imipramine and fluoxetine are equivalent in terms of overall treatment costs, efficacy, and quality of life. In a randomized, controlled trial, patients with newly diagnosed depression ( $n=536$ ) were prescribed either fluoxetine or a tricyclic antidepressant (imipramine or desipramine) and assessed at 1, 3, and 6 months for both efficacy of the antidepressant regimen as measured by the Hamilton Depression Rating Scale and the Hopkins Symptom Checklist and quality of life. Drug cost and total health care costs were also measured. Clinical efficacy and quality of life were similar between the two groups; however, patients treated with fluoxetine had fewer adverse effects, were less likely to require a change in their medication, and had less outpatient visits. Although drug costs were higher, total treatment costs were slightly lower for the fluoxetine group; however, this difference was not statistically significant [1119].

d) Controlled studies have demonstrated that oral fluoxetine in doses of 40 to 80 milligrams daily is as effective as imipramine 150 to 250 milligrams daily in the treatment of major depression [1120][1121] [1122]. Fluoxetine was as effective as imipramine doses of 150 to 300 milligrams/day [1123]. However, in one report [1124], fluoxetine was reported superior to imipramine in several depression scales in a 5-week controlled study involving 40 depressed outpatients. In all studies, the incidence of side effects (anticholinergic effects, dizziness, drowsiness, dry mouth, cardiovascular effects) was less with fluoxetine as compared with imipramine; fluoxetine was associated with a greater incidence of anxiety or nervousness, insomnia, and excessive sweating. In another study, excessive sweating (as well as nausea) was higher with fluoxetine than imipramine [1121]. Of significance, weight loss has occurred during fluoxetine therapy, as compared to generally no change in body weight or increases in weight with imipramine. The onset of antidepressant action of each drug has been similar, generally within one week.

e) Imipramine and fluoxetine had similar efficacy in multicenter, double-blind, placebo-controlled, outpatient studies comparing the treatment of major depressive disorder [1121]. Five hundred forty patients were randomly assigned to receive either fluoxetine 60 to 80 milligrams daily, imipramine 150 to 300 milligrams daily (the majority of patients), or placebo. Patients were treated for up to 6 weeks in double-blind fashion. Imipramine and fluoxetine were both superior to placebo on all measures (Hamilton Psychiatric Rating Scale for Depression total, Raskin Severity of Depression Scale, Clinical Global Impressions Severity of Illness Scale, Global Improvement and secondary symptom measures). Fluoxetine and imipramine were similarly effective on all general measures of improvement. Anorexia and nausea occurred to a significantly higher degree in fluoxetine-treated patients; constipation, dizziness, drowsiness, dry mouth, somatosensory disturbances, and excessive sweating were reported more frequently with imipramine.

f) The efficacy and safety of fluoxetine and imipramine was compared in 40 depressed outpatients in a double-blind, 5-week parallel trial [1124]. Fluoxetine was given in doses increasing from 20 to 40 milligrams daily, then to 60 milligrams daily, during the first week; imipramine doses were increased from 75 to 100 milligrams daily, then to 125 milligrams daily. During the second and third weeks, the maintenance dose of each drug was determined, with fluoxetine being given in doses up to 80 milligrams daily and imipramine up to 300 milligrams daily. During the fourth and fifth weeks of the study, the maintenance dose was achieved; the maintenance dose for most fluoxetine patients was 60 milligrams daily, and 175 or 200 milligrams daily for imipramine. Fluoxetine was reported superior to imipramine in the total



Hamilton Psychiatric Rating Scale for Depression, as well as the HAM-D scales for anxiety/somatization, retardation and sleep disturbance. [Fluoxetine](#) was also reported more beneficial than [imipramine](#) in the Raskin Severity of Depression Scale and Covi Anxiety Scale. However, for the HAM-D total score, and the Raskin and Covi scales, [fluoxetine](#) was statistically superior to [imipramine](#) only during the last week of the study (week 5). The Clinical Global Impressions demonstrated the superiority of [fluoxetine](#) over [imipramine](#) for severity of depression but not global improvement. Weight loss (average, 3.8 pounds) occurred with [fluoxetine](#) during treatment, with an increase in weight being seen with [imipramine](#) (average, 0.7 pounds). Heart rate increased significantly with [imipramine](#), as compared to slight decreases with [fluoxetine](#). Blood pressure decreased with [fluoxetine](#) as compared with increases with [imipramine](#), and [fluoxetine](#) was associated with a lesser degree of gastrointestinal disturbances, dizziness, and drowsiness. Dry mouth occurred in one of 20 [fluoxetine](#) patients and in 9 of 20 imipramine-treated patients, with nervousness occurring in three fluoxetine-treated patients and in two imipramine-treated patients.

#### 4.6.AD] [Fluvoxamine](#)

##### 4.6.AD.1] Depression

a) SUMMARY: [Fluvoxamine](#) and [imipramine](#) appear to be equally efficacious in the treatment of depression [1237][1238][1239][1240]; (March, 1990)[1241].

b) [Fluvoxamine](#) demonstrated a trend toward superiority over [imipramine](#) in treating 63 patients with [major depression](#) during a 4- to 6-week, randomized, placebo-controlled, double-blind study [1237]. All drugs were started at 50 milligrams/day, and were gradually increased to a maximum of 300 mg/day. The mean daily dose of [fluvoxamine](#) at the the end of the study was 207 mg, and 192 mg for [imipramine](#). At the end of the study, the total Hamilton Rating Scale for Depression (HAM-D) score had decreased by 75%, 55%, and 6% in the [fluvoxamine](#)-, [imipramine](#)-, and placebo-treated groups, respectively. At the end of the study there were 8, 3, and 1 responders from the [fluvoxamine](#), [imipramine](#), and placebo groups, respectively. Only 1 patient in each active treatment group withdrew from the study because of adverse effects.

c) [Fluvoxamine](#) was comparable to [imipramine](#) in antidepressant activity during a 4-week, double-blind, multicenter study of 151 patients [1238]. Drug therapy was administered in twice daily dosing in the range of 100 to 300 milligrams daily for [fluvoxamine](#) and 50 to 200 milligrams daily for [imipramine](#). At the end of the study there was a mean improvement in the Hamilton Rating Scale for Depression (HAM-D) of 67.2% in the fluvoxamine-treated group and a 62.1% improvement in the imipramine-treated group. A similar improvement was detected with both drugs on the Clinical Global Impression Scale. At the end of the study, the mean daily dose of [fluvoxamine](#) was 221 mg and 112 mg for [imipramine](#). A total of 37 patients withdrew from the study prematurely; 19 on [fluvoxamine](#) and 18 on [imipramine](#). The reasons for early withdrawal appeared to be similar between both drugs.

d) [Fluvoxamine](#) and [imipramine](#) were comparable in efficacy for the treatment of depression in 36 patients diagnosed with unipolar or [bipolar depression](#) during a 4- to 6-week, randomized, double-blind study [1239]. Both medications were administered at bedtime with a maximal dosage range between 150 to 225 milligrams/day. In the unipolar depressed fluvoxamine-treated patients, 92% were judged "improved" at the end of the study compared to 81% of the [imipramine](#) group. However, the imipramine-treated group appeared to have a higher percent of patients rated as "much" or "very much" improved, 75% compared to 54% of the [fluvoxamine](#) group.

e) A double-blind comparative study of [fluvoxamine](#) and [imipramine](#) was carried out in 20 outpatients with [depressive disorder](#). Patients received randomly-assigned medication over a 4-week period in a dosage range of 50 of 300 mg given in 2 divided doses. There was a significant symptom severity reduction in both groups at the end of 4 weeks, and [fluvoxamine](#) was more effective than [imipramine](#) in reducing suicidal ideas and anxiety/somatic symptoms. Anticholinergic-type adverse reactions predominated for [imipramine](#) and gastrointestinal effects for [fluvoxamine](#) [1242].

f) In a 6-week, double-blind, placebo-controlled, variable-dose study assessing the comparative antidepressant efficacy of [fluvoxamine](#) (FLU), [imipramine](#) (IMI), and placebo (PBO), 45 patients with [major depressive disorder](#) were evaluated for response and side effects. Dosage ranged between 100 to 300 milligrams/day for active medications. No statistically significant differences between either the FLU (N=17) and PBO or the FLU and IMI groups were found. Side effects were present in all three groups: IMI(N=18): constipation (83%), dry mouth (55%), and sweating, dizziness, and nausea, all 39%. FLU(N=18): diarrhea, headache, dry mouth, all 41%, nausea (35%), and flatus (29%). PBO(N=18): [pruritus](#) (29%), nausea (23%), headache (18%), asthenia and somnolence, both 12%. This study revealed a high placebo response, with a 50% improvement at week 6. Thus, it is difficult to show differences from active medication unless the study is carried out for a longer time. In addition, the numbers of patients are too small to detect a true difference. Second, patients seemed to either respond or not respond to FLU, while the response to IMI appeared to be more graded. This may reflect a subgroup of depressed patients that have a serotonin-deficient type of depression [1241].

g) Other double-blind, placebo-controlled studies comparing [imipramine](#) and [fluvoxamine](#) have only demonstrated slightly more improvement in depression with either drug when compared with placebo [1243][1244].

#### 4.6.AD.2) Adverse Effects

a) SUMMARY: [Fluvoxamine](#) produces less cardiovascular and anticholinergic adverse effects than [imipramine](#); however, nausea and vomiting are more common with [fluvoxamine](#) therapy [1233][1234][1235][1236].

b) Adverse effects data was pooled from the results of 10 double-blind, placebo-controlled trials comparing [fluvoxamine](#) (n=222) with [imipramine](#) (n=221) [1233]. Anticholinergic effects such as dry mouth, dizziness/syncope, sweating, and abnormal accommodation were much more prevalent in patients receiving [imipramine](#). Nausea/vomiting was the only adverse effect to be much more prevalent in the [fluvoxamine](#)-treated patients.

c) The cardiac effects of tricyclic antidepressants were compared with [fluvoxamine](#). The major cardiac adverse effects observed with tricyclic antidepressants include postural hypotension, heart rate increase, and slight prolongation of the intraventricular conduction time and QT interval. The only cardiac effect observed with [fluvoxamine](#) was a statistically, but not clinically, significant slowing of heart rate [1234].

d) [Fluvoxamine](#) produced less [psychomotor impairment](#) than [imipramine](#). [Fluvoxamine](#) was superior to [imipramine](#) 75 milligrams in regards to concentration, reaction time, mood, psychomotor activity, and affectivity. Following the administration of [fluvoxamine](#) 75 milligrams to 10 healthy volunteers, psychometric tests demonstrated a tendency towards an improvement in psychomotor activity, concentration, attention, after-effect, and mood and a significant increase in critical flicker fusion frequency when compared to placebo [1235].

#### 4.6.AE] Gepirone

##### 4.6.AE.1] Depression

a) Gepirone extended-release 10 to 60 mg daily was only marginally superior to placebo at some time points over 8 weeks, and tended to be less effective than [imipramine](#) 50 to 300 mg daily in one double-blind study involving patients with [major depression](#) [1096].

#### 4.6.AF] [Haloperidol](#)

##### 4.6.AF.1] [Schizophrenia](#)

a) **Haloperidol** was compared with placebo, **chlorpromazine**, **diazepam**, and **imipramine** as prophylactic agents to prevent **relapse** of schizophrenic patients. At the end of the three-year trial, **haloperidol** and **chlorpromazine** significantly prolonged remission as compared to the other three treatments. Daily doses of **haloperidol** were 3 milligrams; **chlorpromazine** doses were 75 mg [1134].

#### 4.6.AG] **Lithium**

##### 4.6.AG.1] **Depression**

a) **Lithium** was more effective in the treatment of unipolar and **bipolar depression** in 63 female in-patients in a double-blind, controlled study. The patients received either **lithium** in doses producing serum levels of 0.8 to 1.2 mmole/L or **imipramine** 150 milligrams/day in divided doses. Improvement occurred more quickly with **imipramine** (between days 1 and 8) than with **lithium** (days 8 to 22); however, all patients treated with **lithium** improved, but not all imipramine-treated patients did so [1245].

#### 4.6.AH] **Lofepramine**

##### 4.6.AH.1] **Depression**

a) A meta-analysis of 7 studies comparing lofepramine (n=372) with **imipramine** (n=372) concluded that lofepramine was comparable with **imipramine** in efficacy and superior in tolerance [1249]. Overall, there was no significant difference between the number of lofepramine-treated patients (64%) and imipramine-treated patients (58%) who improved during the trials that ranged from 4 to 8 weeks. Significantly fewer patients reported side effects with lofepramine than **imipramine** (55% vs 68%; p less than 0.0001). Lofepramine doses ranged from 25 to 225 milligrams/d, and **imipramine** doses ranged from 25 to 150 milligrams/d.

b) Lofepramine is a tricyclic antidepressant that is structurally similar to **imipramine**, but has an improved lipophilicity [1250].

c) Lofepramine and **imipramine** had similar efficacy in a randomized, double-blind, placebo-controlled clinical trial [1250]. Of the 139 patients initially enrolled in the study, 89 completed the full 6 weeks of treatment (34 lofepramine, 34 **imipramine**, and 21 placebo). Dropout rates for the lofepramine and **imipramine** group were similar when compared for treatment failures and side effects. There was a significantly high placebo dropout rate, with the majority of patients dropping out due to a lack of clinical efficacy. Lofepramine and **imipramine** were both significantly better than placebo in the treatment of primary depression. There was no significant difference between the **imipramine** and lofepramine group with regards to efficacy. Lofepramine therapy was associated with significantly lower incidence of severe and/or moderate side effects (40.9% compared with 66.7% observed in the **imipramine** group), and a lower incidence of side effects in general.

d) Lofepramine and **imipramine** were compared in a double-blind placebo-controlled study involving 158 depressed outpatients. Both drugs were equally efficacious and superior to placebo therapy. Lofepramine therapy produced a lower incidence of sedation and anticholinergic effects than **imipramine** therapy [1251].

#### 4.6.AI] **Maprotiline**

##### 4.6.AI.1] **Depression**

a) SUMMARY: **Maprotiline** is considered very similar to **imipramine** in therapeutic efficacy [1265][1266][1267][1268][1269][1270][1271][1272]. **Maprotiline** therapy may be associated with a quicker onset of action [1265]; (Clayhorn, 1977).

b) **Maprotiline** 50 milligrams orally 3 times/day was administered to a maximum of 300 mg/day or **imipramine** 50 to 300 milligrams orally per day to 341 patients with **manic depressive illness**. Patients ranged in age from 19 to 64 years and received treatment for 4 weeks. Improvement was based on

Hamilton's and Self-Rating scales. Sixty-seven percent of the patients receiving [maprotiline](#) were reported as improved compared with 66% of the patients who received [imipramine](#). Central nervous system effects, dry mouth, tremor, blurred vision, and gastrointestinal effects were reported but were significantly less in the maprotiline-treated group [1273].

c) [Maprotiline](#) was superior to [imipramine](#) in a double-blind, randomized controlled trial of 25 inpatients with primary [depressive disorder](#) [1271]. The dose of [maprotiline](#) and [imipramine](#) was 50 milligrams three times a day for five days followed by a flexible dosing schedule for three weeks. Results of the 16 patients completing the trial showed the Hamilton Depression Scores for the [maprotiline](#) group to be significantly better (p less than 0.05) than those for the [imipramine](#) group on day three of the trial. The Zung Depression Scale favored [maprotiline](#) (p less than 0.01) on day seven and at the end of the treatment (p less than 0.10). Overall rating of global impression (p less than 0.05) and global improvement at endpoint (p less than 0.10) indicated [maprotiline](#) to be superior to [imipramine](#). Dropouts from the study included five [maprotiline](#) patients, three leaving the hospital against medical advice, one improving so as to warrant discontinuation of therapy, and one due to inadequate response. Two patients from the [imipramine](#) group dropped out due to toxicity, one due to deterioration after initiation of treatment, and one because of physician intervention. Side effects were prevalent on day three but decreased in incidence by day 14. Common complaints in both groups were dry mouth, blurred vision, drowsiness, and nasal congestion. Nausea was reported only in the [imipramine](#) group.

#### 4.6.AJ] Melitracen

##### 4.6.AJ.1] Depression

a) Four-week, double-blind trial; 29 patients with chronic schizophrenic or [neurotic depression](#); melitracen 75 to 200 milligrams (mg)/day vs [imipramine](#) 50 to 150 mg/day. Brief Psychiatric Rating Scale, Hamilton Psychiatric Rating Scale and Clinical Global Impression: some improvement in both treatment groups, efficacy of [imipramine](#) superior to melitracen (not statistically significant). Melitracen better tolerated than [imipramine](#): 46 adverse effects (drowsiness, dry mouth, increased perspiration, tinnitus, agitation) for melitracen vs 69 for [imipramine](#). Quicker average onset of therapeutic effect for melitracen: 1.7 weeks vs 2.2 weeks [1246].

#### 4.6.AK] Methscopolamine

##### 4.6.AK.1] Nocturnal enuresis

a) [Methscopolamine](#) is ineffective in the treatment of [enuresis](#). In a study with 40 severely enuretic boys, [methscopolamine](#) bromide was used to determine whether some subgroups of enuretic children might respond to the peripheral blockade of muscarinic receptors. The effects of treatment with [imipramine](#), [desipramine](#), [methscopolamine](#) bromide, and placebo were compared; the tricyclic antidepressants were superior to [methscopolamine](#) and placebo [1248].

#### 4.6.AL] Mianserin

##### 4.6.AL.1] Depression

a) Studies to date suggest that there is no significant difference in overall efficacy between [imipramine](#) and mianserin in the treatment of depression in both inpatients and outpatients [1220][1221][1222]. However, several deficiencies are apparent in clinical trials to date, and 1 study has indicated that improvements seen with mianserin and [imipramine](#) were equivalent to those observed with placebo [1223]. (However, these patients were treated for only 3 weeks, which may have been insufficient time for therapeutic effects from either drug to occur).

**b)** Mianserin therapy (20 to 60 milligrams/day) in elderly depressed patients (n=50, age 60 to 80 years) is as efficacious as [imipramine](#) therapy (75 to 150 milligrams/day) [1224]. The incidence of dry mouth, dizziness, faintness, and weakness was greater in the [imipramine](#) group than in the mianserin group, however the total number of side effects reported by each group was not significantly different. From these results the authors concluded that mianserin may be preferred to [imipramine](#) in the treatment of depression in elderly patients because of its lower incidence of side effects. However, a larger number of mianserin treated patients withdrew from the study due to confusion, worsening of the condition, or lack of effect. Considering this, it is too early to conclude that mianserin is superior to [imipramine](#) in the treatment of depression in the elderly.

#### 4.6.AL.2] Nocturnal [enuresis](#)

**a)** [Imipramine](#) was superior to mianserin and placebo in achieving dry nights and reducing wetness scores (p less than 0.05); mianserin was not superior to placebo. This was a multicenter, randomized, double-blind study involving 80 children [1225].

### 4.6.AM] Milnacipran

#### 4.6.AM.1] Depression

**a)** SUMMARY: Milnacipran offers no efficacy advantage over tricyclic antidepressants

**b)** 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 [1226][1227][1228][1229][1230][1231]. A more rapid onset of action has been observed with [clomipramine](#) and [amitriptyline](#) [1227][1231].

**c)** 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 [1229][1228], and this appears in manufacturer product information. However, statistical significance between treatments was not demonstrated [1229].

### 4.6.AN] Moclobemide

#### 4.6.AN.1] Depression

**a)** SUMMARY: Moclobemide and [imipramine](#) have been similarly effective in the treatment of depression; adverse effects have generally been greater with [imipramine](#).

**b)** Moclobemide 300 to 600 milligrams orally daily has been as effective as [imipramine](#) 100 to 200 milligrams orally daily in the treatment of endogenous and non-endogenous depression in controlled clinical trials [1212][1213][1214][1215][1216][1217][1218][1219]. However, a trend (not statistically significant) toward the superiority of [imipramine](#) over moclobemide in treating [reactive](#) or [neurotic depression](#) has been observed by some investigators [1213][1215]. A slightly more rapid response was reported with moclobemide in 1 study [1219].

**c)** In 1 study, the response rate to [imipramine](#) and moclobemide was similar in both males and females. However, both agents tended to be less effective in depressed patients over 60 years of age as compared with patients under 60 [1213].

**d)** Moclobemide and [imipramine](#) were equally efficacious in a placebo-controlled, 6-week study [1215]. In 1 of the largest trials to date (n=490) involving patients with a [major depressive episode](#) (50% with [endogenous depression](#)), a 52% reduction in the average Hamilton Rating Scale for Depression (HRSD) was observed with moclobemide 300 to 600 milligrams daily, as compared with 28% with placebo, during 6 weeks of treatment. [Imipramine](#) (100 to 200 milligrams daily) was included for comparison in this study, and was as effective as moclobemide, producing a 56% reduction in HRSD score. Based upon final



assessments of efficacy by the investigators, good to very good responses were reported in 70% of patients treated with moclobemide, 70% treated with [imipramine](#), and 28% treated with placebo. When subgroups of patients with endogenous and non-endogenous depression were analyzed, both drugs were similarly effective and superior to placebo in each subgroup. Overall tolerability assessments favored moclobemide over [imipramine](#) [1215].

#### 4.6.AN.2) Adverse Effects

a) Adverse effects have generally been less with moclobemide compared to [imipramine](#), particularly dry mouth, constipation, tremor, sweating, and blurred vision [1217].

#### 4.6.AO] [Moricizine](#)

##### 4.6.AO.1] [Cardiac dysrhythmia - Myocardial infarction with complication](#), Post

a) [Encainide](#) and [flecainide](#) were more effective in suppressing [ventricular arrhythmias](#) than [moricizine](#), [imipramine](#), and placebo during the dose titration phase of a 1-year, multicenter, randomized, double-blind and placebo-controlled study of 502 patients [1274]. Patients were eligible for this study if they had an acute [myocardial infarction](#) within 6 to 60 days of entrance to the study, were less than 75 years of age and demonstrated either an average of 10 or more [ventricular premature complexes](#) (VPCs) per hour or 5 or more episodes of unsustained [ventricular tachycardia](#) (3 to 9 consecutive VPCs with a rate of 100/minute or more) during a 24-hour [ambulatory ECG](#) recording. The total daily doses of the study drugs ranged from 105 to 180 milligrams for [encainide](#), from 200 to 400 milligrams for [flecainide](#), from 150 to 375 milligrams for [imipramine](#), and from 600 to 900 milligrams for [moricizine](#). Efficacy was defined as 70% or more suppression in VPC frequency and more than 90% suppression of runs of VCP when compared to baseline. The efficacy rates were 83% for [flecainide](#), 79% for [encainide](#), 66% for [moricizine](#), 52% for [imipramine](#), and 37% for placebo during the dose titration phase of the study. The incidence of adverse effects was 49% for [encainide](#), 55% for [flecainide](#), 67% for [imipramine](#), 64% for [moricizine](#), and 60% for placebo. [Imipramine](#) was the drug most associated with patient withdrawal due to adverse effects. This study did not address VPC suppression efficacy at the 1-year follow-up.

#### 4.6.AP] [Nefazodone](#)

##### 4.6.AP.1] Depression

a) [Nefazodone](#) was comparable overall to [imipramine](#) in a 6-week double-blind, placebo-controlled study involving 45 patients with [major depression](#). Average doses at the end of 6 weeks were 180 and 158 milligrams daily, respectively. However, both drugs were not always significantly superior to placebo in improving Hamilton Rating Scale for Depression (HAM-D) scores, and [imipramine](#) tended to be superior to [nefazodone](#) on the visit-wise (observed case) analysis of HAM-D; in this latter analysis, [imipramine](#) was statistically superior to placebo at weeks 4 through 6 of treatment, whereas [nefazodone](#) was significantly more effective only at week 5. Neither agent proved statistically more effective than placebo on the Clinical Global Impressions scale (clinician's rating). Although adverse effects tended to be less with [nefazodone](#), specific effects induced by either agent were not presented. This study did not provide a direct statistical comparison of [imipramine](#) and [nefazodone](#) [1278].

b) Meta-analysis of 6 placebo-controlled, double blind studies showed that [nefazodone](#) and [imipramine](#) were effective in treating [major depression](#) and the accompanying symptoms of anxiety, and [nefazodone](#) was superior to [imipramine](#) in the treatment of agitation [1279]. [Nefazodone](#) (100 to 600 milligrams/day; mean endpoint dose=391 milligrams; n=184), [imipramine](#) (25 to 300 milligrams/day; mean endpoint dose=178 milligrams; n=288), and placebo (n=345) were compared in four 6-week and two 8-week studies. Both agents were significantly better than placebo in treating depression. Anxiety symptoms were significantly improved by both agents compared with placebo; [nefazodone](#) resulted in improvement in



both psychic anxiety and somatic anxiety as measured by the HAM-D scale, whereas [imipramine](#) had no effect on somatic anxiety. [Nefazodone](#) was significantly better than placebo in relieving agitation at weeks 1 and 3 through endpoint; [imipramine](#) showed a significant difference from placebo only at endpoint.

c) In a randomized, double-blind, placebo-controlled trial, [nefazodone](#) and [imipramine](#) were compared in 180 outpatients with depression [1280]. [Nefazodone](#) was comparable in antidepressant efficacy to [imipramine](#); significant improvement was evident in self-report anxiety symptoms as early as week 1 for [nefazodone](#) patients in either dose range. The therapeutic dose range of [nefazodone](#) was found to be 100 to 500 milligrams/day, with most patients ultimately receiving 400 to 500 milligrams/day. In this trial, nefazodone-treated patients experienced significantly fewer adverse events than [imipramine](#). The dose of [imipramine](#) ranged from 50 to 250 milligrams/day with the average dose being 214.4 milligrams/day.

#### 4.6.AP.2) Adverse Effects

a) With acute phase- or long-term use of therapeutic doses of [nefazodone](#) or [imipramine](#) for depression, significantly more imipramine-treated patients than nefazodone-treated patients experienced clinically significant weight gain (greater than 7% of body weight). A retrospective analysis of pooled data from 3 studies comparing [nefazodone](#) (n=225) and [imipramine](#) (n=224) showed that, at some time during the long-term phase of treatment, 9.5% of those taking [nefazodone](#) and 24.5% of those taking [imipramine](#) had clinically significant weight gain. At study endpoint, 2.9% and 19.7%, respectively (p=0.001) showed weight gain. Percentages of patients with weight gain during acute-phase treatment were 0.9% for [nefazodone](#) and 4.9% for [imipramine](#) (p=0.02) [1277].

#### 4.6.AQ] Nomifensine

##### 4.6.AQ.1] Depression

a) SUMMARY: Nomifensine and [imipramine](#) appear similarly effective in the treatment of depression in inpatients and outpatients, including the elderly; comparative doses for each have been 75 to 150 milligrams/day. In general, toxicity of nomifensine is less than [imipramine](#) [1258][1259][1260][1261][1262][1263].

b) Nomifensine was as effective as [imipramine](#) in 20 patients with endogenous over-reactive depression [1261]. Patients received 147.9 milligrams (mean) nomifensine daily or 158.3 milligrams (mean) [imipramine](#) daily in a 6-week standard, controlled, double-blind study. The incidence of anticholinergic side effects was lower with nomifensine than [imipramine](#). Nomifensine and [imipramine](#), each in doses of 75 to 150 mg/day for 6 weeks, were equally effective in the treatment of 30 depressed patients. Autonomic side effects with nomifensine occurred less frequently than with [imipramine](#) [1262].

c) Nomifensine was equally efficacious as [imipramine](#) in 28 patients who received a daily dose of 150 to 200 milligrams over a period of 20 to 30 days. Side effects associated with nomifensine were lower than those associated with [imipramine](#) [1264].

d) Based on the Hamilton rating scale and the [Beck depression inventory](#), nomifensine and [imipramine](#) were equally efficacious in the treatment of 30 outpatients with depression. Side effects of nomifensine and [imipramine](#) were the same [1263].

e) Nomifensine in average doses of 150 milligrams orally daily was reported similarly effective as [imipramine](#) (150 mg daily) in the treatment of depression in outpatients in a 4-week controlled study [1259]. However, toxicity (primarily dry mouth and sedation) was more frequent in [imipramine](#) patients.

#### 4.6.AR] Nortriptyline

##### 4.6.AR.1] Depression

a) Most studies have indicated that there are no significant differences between [nortriptyline](#) and other antidepressant drugs of the tricyclic category such as [amitriptyline](#) [1195][1196][1197][1198][1199], [desipramine](#) [1200][1201][1202][1203], [protriptyline](#) [1200], and [imipramine](#) [1204].

#### 4.6.AR.2) Efficacy

a) The effects of [imipramine](#) and [nortriptyline](#) on left ventricular function and blood pressure were studied during a dose-ranging study of 20 patients with [ventricular arrhythmias](#). Ten consecutive patients with more than 30 [ventricular premature depolarizations](#) (VPDs) were treated with [imipramine](#) starting at 1 milligram/kilogram/day, increased by 1 mg/kg/day every second day, to a maximum dose of 5 mg/kg/day. [Nortriptyline](#) was administered to 10 similar patients beginning at 0.5 milligram/kilogram/day, increased by 0.5 mg/kg/day every third day to a maximum of 3.5 mg/kg/day. The 2 groups were similar in terms of age, sex distribution, etiology of [heart disease](#) and NYHA functional class. At a mean effective dose of 210 mg, [imipramine](#) suppressed VPDs by 74%; VPDs were suppressed 85% by a maximally effective [nortriptyline](#) dose of 100 mg. Ejection fraction was slightly decreased with [imipramine](#) (from 33% to 31%) and with [nortriptyline](#) (from 43 to 42%). Mean decreases in orthostatic systolic pressure were greater following [imipramine](#) (26 mmHg) than after [nortriptyline](#) (14 mmHg); no significant change in supine systolic or diastolic blood pressure was noted after either drug. No significant relationship between change in standing systolic blood pressure and daily dose, plasma drug concentration, or NYHA functional class could be demonstrated with either drug. Changes in standing systolic pressure were related to patient age with patients over 50 years old experiencing greater reductions in systolic pressure following administration of both drugs. To determine if real differences exist between [imipramine](#) and [nortriptyline](#) in terms of antiarrhythmic efficacy, studies in cardiac patients who are matched, crossed-over, and randomized to double-blind treatment are needed [1194].

#### 4.6.AS) [Paroxetine](#)

##### 4.6.AS.1) Anxiety

a) In an uncontrolled trial, [paroxetine](#) and [imipramine](#) were as effective as 2-chlorodesmethyldiazepam, a benzodiazepine, for treating [generalized anxiety disorder](#) [1293]. Patients (n=81) received [paroxetine](#) 20 milligrams(mg)/day, [imipramine](#) 50 to 100 mg/day, or 2-chlorodesmethyldiazepam 3 to 6 mg/day for 8 weeks. Over the first 2 weeks, patients treated with 2-chlorodesmethyldiazepam showed greater improvement; however, after 4 weeks for [paroxetine](#) and 8 weeks for [imipramine](#), the anti-depressants were more effective. Adverse effects consisted primarily of anticholinergic effects for [imipramine](#), nausea for [paroxetine](#), and drowsiness for 2-chlorodesmethyldiazepam. Larger, blinded, controlled clinical trials are needed to confirm the results of this study.

##### 4.6.AS.2) [Bipolar disorder](#), depressed phase

a) Neither [paroxetine](#) nor [imipramine](#) was more effective than placebo in treating [BIPOLAR DEPRESSION](#) in patients stabilized on [lithium](#) if their serum [lithium](#) levels were above 0.8 milliequivalents per liter (meq/L). However, patients whose serum [lithium](#) concentration was less than 0.8 meq/L showed greater improvement with 8 weeks of antidepressant treatment than with placebo treatment (p=0.05 for [paroxetine](#), p=0.04 for [imipramine](#)). In a double-blind study, patients were stratified according to serum [lithium](#) concentration and then randomized to receive [paroxetine](#) (n=35), [imipramine](#) (n=39), or placebo (n=43) for 10 weeks. Among all completers of the study, therapeutic response (Hamilton depression scale scores of 7 or less) was achieved by 56%, 48%, and 54% of patients receiving [paroxetine](#), [imipramine](#), and placebo, respectively. Adverse events accounted for study discontinuation in 1 patient in the [paroxetine](#) group (3%), 12 in the [imipramine](#) group (30%), and 5 in the placebo group (12%). No patient in the

paroxetine group experienced induction to mania, whereas 3 patients treated with imipramine and 1 treated with placebo developed treatment-emergent mania [1294].

#### 4.6.AS.3] Depression

a) SUMMARY: Paroxetine, a selective serotonin reuptake inhibitor, and imipramine appear to be similarly effective in the treatment of major depression. The decision as to which drug to use should be based on patient-related characteristics (eg, anxiety disorders, sleep disturbances, cardiovascular disease), potential drug interactions, and side effects.

b) Paroxetine, imipramine, and placebo were compared in 120 outpatients with moderate-to-severe major depression (DSM-III) [1295]. Following a 4- to 14-day single-blind, placebo washout period, patients were assigned to receive either paroxetine, imipramine, or placebo for 6 weeks. The dose of paroxetine and imipramine could be increased to a maximum of 50 milligrams and 275 milligrams daily, respectively. Paroxetine was superior to placebo in 5 of 6 measures evaluated (HAMD scale, Raskin depression scale, MADRS, CGI scale, Covi anxiety scale); no improvement was observed as compared to placebo in the 56-item Symptom Checklist (SCL-56). Imipramine was also statistically superior to placebo on HAMD, Raskin, MADRS, and the CGI scale, but not on the Covi anxiety scale or the SCL-56. The only outcome measure that improved to a significantly greater degree with paroxetine was the HAMD total score. A high number of patients discontinued therapy (approximately 50%), which limits evaluation of efficacy. If only the patients completing the study are considered, imipramine and paroxetine appear to be equally effective. Based upon the number of dropouts due to adverse effects, paroxetine appeared to be better tolerated than imipramine: 10% versus 30%. The most common adverse effects with paroxetine were sedation and gastrointestinal effects, whereas anticholinergic adverse effects (dry mouth, constipation, urinary symptoms) were the most common with imipramine. However, a detailed incidence of all adverse effects was not provided, making it difficult to fully compare these agents.

c) Paroxetine was more effective than placebo in the short-term (6-week) treatment of depression; however, paroxetine was less effective than imipramine. The study was double-blinded and 122 patients with a major depressive disorder were randomized to receive either paroxetine (dose range 20 to 50 milligrams/day), imipramine (dose range 65 to 275 milligrams/day) or placebo. At the end of the study, the imipramine-treated patients demonstrated consistently better scores, both objective and subjective, on all depression rating scales when compared to paroxetine. Overall there was a 64% response rate to imipramine, a 48% response rate to paroxetine, and a 33% response rate to placebo [1296].

d) A multicenter, double-blind, placebo-controlled evaluation of paroxetine and imipramine in the outpatient treatment of major depression was conducted [1297]. After a 4- to 14-day placebo run-in period, patients were randomized to their treatment groups; 240 to the paroxetine group, 237 to the imipramine group, and 240 to the placebo group. Therapy was started at 20 milligrams paroxetine and 80 milligrams imipramine. Dosage adjustment, if necessary, was done at weekly intervals over the six-week treatment phase. Drop-out rates were high for all groups; paroxetine 42.5%, imipramine 53.3%, and placebo 53.6%. Lack of efficacy (10%, 7%, and 33%, respectively) and side effects (23%, 36%, and 9%, respectively) were the most common reasons stated for dropping out of the study. Imipramine and paroxetine were equally superior to placebo and produced similar efficacy results. However, paroxetine therapy was associated with less sedation, cardiovascular, and anticholinergic side effects.

e) Newer clinical trials have continued to support the previous findings that imipramine and paroxetine are similar in effectiveness. The major differences between the two compounds are the frequency of side effects, types of side effects, and frequency of patients withdrawing from the clinical trials secondary to side effects from the study medications. In all cases paroxetine therapy is better tolerated and associated with lower withdrawal rates [1298][1299]; (Arminen et al, 1994).

f) A 6-week, double-blind study was continued for 1 year by crossing over all patients who had failed to respond to initial treatment to the other drug [1300]. Patients first treated with placebo were crossed over to paroxetine (n=19). A total of 15 patients initially treated with paroxetine switched to imipramine, while

10 imipramine patients were switched to paroxetine. Of the patients who initially failed on paroxetine, 73% responded to imipramine, while 50% of the patients who initially failed on imipramine responded to paroxetine. Similar studies have shown paroxetine to be at least as effective as imipramine with fewer side effects [1301][1302][1303][1304].

#### 4.6.AT] Phenelzine

##### 4.6.AT.1] Depression

a) SUMMARY: Phenelzine and imipramine have been found to be equally effective in treating depression and anxiety, although imipramine was more effective in the treatment of hostility and paranoia, whereas phenelzine was more effective in treating panic attacks [1178][1179][1180]. Phenelzine therapy is superior to imipramine in the treatment of atypical depression [1181][1182][1183][1184][1185][1186][1187]. In one case report, phenelzine treatment was found to relieve the symptoms of obsessive-compulsive disorder (OCD) when treatment with amitriptyline and imipramine had failed.

b) Imipramine (median, 150 milligrams daily) had comparable efficacy with phenelzine (median, 75 milligrams daily) in the treatment of major depression in a 5-week, controlled, outpatient study. However, phenelzine was reported superior to imipramine in patients also presenting with panic attacks [1179].

c) Phenelzine, imipramine, and placebo were compared in a double-blind study in 74 patients with probable atypical depression [1183]. Sixty patients completed the study. Dropout was similar among treatment groups. At six weeks, 28% of the placebo-treated group, 50% of imipramine group, and 71% of the phenelzine group were classified as responders. Patients with reactive mood and only one associated symptom appeared to get more benefit with phenelzine. During the next 6 weeks of the study, 41% of the placebo patients, 21% of the imipramine patients, and 7% of the phenelzine patients experienced a relapse, despite continued drug therapy. Patients with definite atypical depression and history of panic attacks responded well to drug therapy; after 6 weeks, response was observed in 60% of the placebo patients, 50% of the imipramine patients, and 64% of the phenelzine patients. Patients with definite atypical depression without a history of panic attacks did not respond as well; after 6 weeks, response was observed in 7% of the placebo group, 44% in the imipramine group, and 83% in the phenelzine group.

d) A comparison of the results of one study were contrasted with previously published data from 180 patients with atypical depression [1183][1184]. Both imipramine and phenelzine were equally effective in the treatment of simple mood reactive depressive patients. Patients with atypical depression tended to respond better to phenelzine than imipramine and 66% that had failed imipramine therapy responded with phenelzine therapy.

e) Replication of a previous study [1183] substantiated the previous finding that phenelzine is superior to imipramine and placebo in the treatment of atypical depression [1185]. This study used the same protocol with minor changes in dose schedule as in the 1988 study and included 90 patients with atypical depression which were not included in the previous study population. Comparison of both groups found no significant difference between either patient population.

f) A six-week comparison of imipramine, phenelzine, and placebo was conducted in 194 nonmelancholic depressed outpatients with features of atypical depression [1182]. The overall response rates was 71% with phenelzine (mean dose was 73 milligrams/day), 48% with imipramine (mean dose was 265 milligrams/day), and 26% with placebo (mean dose was 5.7 tablets/day). Patients with dysrhythmic disorder tended to respond better than those with major depression. An inverse relationship was found in the placebo group between response and chronicity of the disorder.

g) Double-blind trials demonstrated that some patients may require chronic treatment with antidepressants to maintain remission from atypical depression. Patients who improved after 6 months of imipramine therapy were randomized to receive either placebo or their same imipramine dose for a further 6 months in a double-blind fashion. A similar double-blind study was done in patients who had been maintained successfully on phenelzine. In the imipramine trial (n=32), the recurrence rate for continued

imipramine (41%) and placebo (47%) was not significantly different. However, in the phenelzine trial (n=28), recurrence rate of 87% in the placebo treated patients was significantly higher (p=0.001) than those continued on phenelzine (23%). Comparison of the results between imipramine and phenelzine is limited by the absence of blinding between the trials and baseline differences, with earlier onset and longer history of depressive illness in the phenelzine group possibly contributing to the high recurrence in those switched from phenelzine to placebo [1188].

#### 4.6.AT.2] Posttraumatic stress disorder

a) A double-blind, placebo-controlled study of 60 male veterans found phenelzine to be better than imipramine in the treatment of combat-induced post-traumatic stress disorder [1189]. Patients were treated with an average dose of 225 milligrams imipramine and 68 milligrams phenelzine for 8 weeks. Dropout rates were high in all three groups (66.7% with placebo, 60.9% with imipramine, and 21.1% with placebo, 60.9% with imipramine, and 21.1% with phenelzine) with the most common reason being failure to return for clinic visits (50%, 50%, and 25%, respectively). At the end of 8 weeks, imipramine and phenelzine produced greater improvement than placebo and phenelzine was demonstrated more effective than imipramine in improving Impact of Event Scale scores and post-traumatic stress disorder symptoms.

#### 4.6.AU] Reboxetine

##### 4.6.AU.1] Depression

a) Reboxetine exhibited similar efficacy to, better tolerability than, and earlier onset of effect than imipramine for the treatment of major depression in a short-term study (6 weeks) [1281]. Patients (n=256) were randomized to treatment with reboxetine 4 milligrams (mg) twice daily or imipramine 50 mg twice daily with the evening dose increased to 100 mg after 3 weeks of treatment. According to scores on the Hamilton Depression rating scale (HAM-D), response rates for patients treated with reboxetine or imipramine were 68.5% and 56.2% (statistically significant difference) respectively, and remission rates at the last assessment were 52% and 45.5%, respectively. On the Clinical Global Impression Severity of Illness and Global Improvement scales (CGI-SI and CGI-GI), the percentage of reboxetine-treated patients classified as "normal" or "borderline" increased more rapidly than the group treated with imipramine, indicating an earlier onset of response. The Montgomery-Asberg Depression Rating Scale (MADRS) demonstrated no difference between the two treatment groups. Incidence rates of adverse events described as probably or definitely related to treatment were 31.9% and 39% for patients treated with reboxetine or imipramine, respectively.

#### 4.6.AV] Ritalin

##### 4.6.AV.1] Depression

a) Ritalin, a serotonin-2 antagonist, was compared with imipramine in a double-blind, placebo-controlled 7-week study in 50 patients with mild chronic depression (dysthymic disorder). At the end of the study imipramine was slightly more effective than ritalin based on the Hamilton Depression Rating Scale and the Zerssen Self-Rating Scale but was associated with a higher frequency of side effects and a greater attrition rate [1283].

#### 4.6.AW] Risperidone

##### 4.6.AW.1] Depression

a) Imipramine was superior to risperidone in patients with major depressive disorder in one double-blind study (n=64) [1282].



4.6.AX] Sertraline

4.6.AX.1] Depression

a) More than 50% of chronically depressed patients who were nonresponders to an antidepressant responded when switched to an antidepressant of another class. Patients who had completed a randomized, 12-week, double-blind trial with either [sertraline](#) or [imipramine](#) for treatment of chronic depression and had failed to respond were switched to the alternate treatment for 12 more weeks of double-blind treatment. Fifty-one patients were switched from [imipramine](#) to [sertraline](#) and 117 from [sertraline](#) to [imipramine](#). Mean dosages at study end were 221 milligrams (mg) per day for [imipramine](#) and 163 mg/day for [sertraline](#). Ten percent of those switched to [sertraline](#) and 25% of those switched to [imipramine](#) dropped out. The difference in dropout rate was mainly due to intolerable adverse effects of [imipramine](#). Those who switched to [imipramine](#) experienced significant reductions in 3 adverse effects but significant increases in 8 adverse effects, whereas those who switched to [sertraline](#) had significant decreases in 6 adverse effects and significant increases in one:

	SERTRALINE TO IMIPRAMINE	IMIPRAMINE TO SERTRALINE
DECREASED INCIDENCE		
Diarrhea	Insomnia	Dry mouth
Abdominal Pain	Somnolence	
	Increased sweating	
	Constipation	
	Dizziness	
	Urinary complaints	
INCREASED INCIDENCE		
Increased sweating	Dry mouth	Insomnia
Constipation		
Dizziness		
Tremor		
Abnormal taste		
Increased appetite		
Urinary complaints		

b) The intent-to-treat response rates were 60% for [sertraline](#) and 44% for [imipramine](#) (p=0.03). Among completers, however, response rates were 63% and 55%, respectively (p=0.16). After averaging across the study weeks and adjusting for completion status, depression type, and baseline value, there were no significant differences between groups in outcomes. The pattern of improvement over time did not differ for the 2 groups [1254].

c) In a double-blind study of [major depression](#) with or without [dysthymia](#), response to [sertraline](#) was highest in women whereas response with [imipramine](#) was highest in men. Patients meeting DSM III-R criteria for chronic [major depression](#) (235 men and 400 women) were randomized to 12-week treatment with [sertraline](#) or [imipramine](#) in a 2:1 ratio. Both drugs were started at 50 milligrams (mg) daily and titrated to a maximum of 300 mg for [imipramine](#) and 200 mg for [sertraline](#). Although the overall response to [sertraline](#) was similar to [imipramine](#), a statistically significant gender and treatment interaction was observed. The highest response rates occurred in women taking [sertraline](#) and in men taking [imipramine](#). More women responded to [sertraline](#) (147/260; 57%) than to [imipramine](#) (61/133; 46%); and more men responded to [imipramine](#) (43/69; 62%) than to [sertraline](#) (73/161; 45%). Gender differences also occurred in the types of adverse events reported, and more women withdrew from the [imipramine](#) group than from the [sertraline](#) group; however, withdrawal rates by men were not significantly different for the 2 drugs. A significant interaction was also seen between menopausal status and treatment. Withdrawal from treatment was highest in premenopausal women taking [imipramine](#) and postmenopausal women taking



[sertraline](#). The mechanism behind these gender differences is unknown, and may relate to interaction of female sex hormones and serotonin activity. [1255]

#### 4.6.AX.2] [Dysthymia](#)

a) [Sertraline](#) and [imipramine](#) are equally effective for the treatment of [dysthymia](#); however, [sertraline](#) is better tolerated. In a randomized trial, [sertraline](#) and [imipramine](#) were compared and evaluated in a group of 416 patients with [early-onset primary dysthymia](#). Outcome was based on response based on clinical evaluation (Hamilton Rate Scale for Depression, Montgomery- Asberg Depression Rating Scale, Hopkins Symptom Checklist) and patient-rated version of the Inventory of Depressive Symptoms. Improvement of scores of Clinical Global Impressions of 1 or 2 (very much or much improved) demonstrated response rates of 59% for [sertraline](#), 64% for [imipramine](#), and 44% for placebo. The mean dose of required for initial response was 89.5 milligrams (mg) for [sertraline](#) and 159.7 milligrams for [imipramine](#) [1256].

b) Of the 416 patients described in the study above by Thase et al, 355 had completed the Tridimensional Personality Questionnaire before and after treatment, and the results revealed that temperament scores improved with improvement in [dysthymia](#). At baseline, temperament in dysthymic patients was abnormal, with higher mean harm avoidance score from the Tridimensional Personality Questionnaire than that reported for a community population. After 12 weeks of treatment, harm avoidance scores decreased significantly, with no significant differences between the [sertraline](#), [imipramine](#), and placebo group. Scores decreased for those achieving remission and those who did not; however, decreases were significantly greater among the remitters. Thus, improvement in temperament was mainly related to disease improvement regardless of treatment. The results revealed some gender and treatment effects, and further studies using multiple measures, rather than the single measure used in this study, would be needed to determine treatment effects on temperament and personality [1257].

#### 4.6.AX.3] Mixed anxiety and [depressive disorder](#)

a) [Imipramine](#) and [sertraline](#) were equally effective in the treatment of anxiety and depression in patients with comorbid [panic disorder](#) and [major depressive disorder](#). In an randomized, multicenter, double-blind study, patients with full Axis I [panic disorder](#) with concurrent [major depressive disorder](#) with a minimum of 4 panic attacks in the 4 weeks prior to screening and a baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of at least 20 received either [sertraline](#) (n=138; 50 to 100 milligrams (mg), mean dose, 65.4 mg/day) or [imipramine](#) (n=69; 100 to 200 mg, mean dose 144.2 mg/day) for 26 weeks. [Sertraline](#) was given at an initial dose of 25 mg/day for 1 week, then titrated to 50 mg/day for 4 weeks, at which time the dose could be increased to 100 mg, if needed. The initial dose of [imipramine](#) was 25 mg/day, increased at weekly intervals to 50 mg, 100 mg, and 150 mg. If needed, the dose could be increased again to 200 mg or reduced to 100 mg. Primary outcome measures were weekly panic attack frequency and MADRS score. [Sertraline](#) and [imipramine](#) produced similar improvements in the mean baseline (28.5 vs 28.7, respectively) to endpoint (11.1 vs 11.2, respectively) total MADRS score and in the mean baseline (7.1 vs 7, respectively) to endpoint (2.9 vs 2.3, respectively) weekly panic attack frequency. However, sertraline-treated patients reported significantly fewer adverse effects as compared with imipramine-treated patients (23% vs 42%, respectively; p=0.005) and fewer discontinued treatment (11% vs 22%, respectively; p=0.04). Nausea and diarrhea was more frequently reported with [sertraline](#) treatment, while dizziness, dry mouth, sweating, tremor, and constipation were more frequent with [imipramine](#) administration [1253].

#### 4.6.AY] [Sotalol](#)

##### 4.6.AY.1] [Ventricular arrhythmia](#)

a) [Sotalol](#) has been shown to be superior to [procainamide](#), [quinidine](#), [mexiletine](#), [propafenone](#), pirlmenol, and [imipramine](#) in its ability to prevent death and the recurrence of [ventricular arrhythmias](#) in selected

patients with ventricular [tachyarrhythmias](#). Patients with a history of [ventricular fibrillation](#) or flutter with inducible, sustained ventricular [tachyarrhythmias](#) (VT) received the study drugs in random order until one was predicted effective by either [Holter monitor](#) assessment or programmed electrical stimulation (PES). Long-term therapy with the first effective drug was followed to one of three primary endpoints: [arrhythmia](#) recurrence, sudden death, or unmonitored syncope. By PES, [sotalol](#) was predicted effective in 35% of a total of 486 patients compared to 16% for all other drugs. Although not significant, Holter assessment predicted [sotalol](#) effective for long-term suppression in 41% versus 45% for all other drugs combined. After two years of follow-up on chronic therapy, compared to the pooled data for all the other drugs, [sotalol](#) had the lowest mortality rate (13% to 22%), lowest VT recurrence rate (30% vs 60%), and lowest drug withdrawal rate (38% compared to 75% to 80%). Since there was no control group, it is unknown whether [sotalol](#) improved survival or identified a population with a good prognosis [1158][1159][1160].

#### 4.6.AZ] [Tranlycypromine](#)

##### 4.6.AZ.1] Depression

a) [Tranlycypromine](#) is superior to [imipramine](#) in the treatment of patients with anergic [bipolar depression](#) [1161]. Fifty-six patients with [bipolar depression](#) (with 73% meeting the criteria for anergic depression) were randomly assigned to treatment with [tranlycypromine](#) 20 to 80 milligrams or [imipramine](#) 100 to 400 milligrams/day in a double-blind comparative study. The mean dose at the end of six weeks was 36.8 mg of [tranlycypromine](#) and 245.5 mg of [imipramine](#). Patients with anergic [bipolar depression](#) who did not respond to therapy in the initial phase (n=16) were then enrolled in a crossover study with the same doses of each drug [1162]. Nine of the 12 patients who were switched to [tranlycypromine](#) responded to therapy and only one out of four patients switched to [imipramine](#) improved. [Hypomania](#) and mania developed with both drugs, but occurred earlier (5.8 weeks vs 9.2 weeks) in those receiving [imipramine](#).

b) In a double-blind study of 137 patients with [psychotic depression](#), [tranlycypromine](#) 10 milligrams three times daily was administered for an average of 22 weeks. Patients were also randomly allocated to receive [phenelzine](#) or [imipramine](#). After 4 weeks of therapy, 47% of [tranlycypromine](#) patients were improved, and after termination of the study 44% were improved. [Tranlycypromine](#) was slightly less effective than [imipramine](#), but more effective than [phenelzine](#) [1163].

#### 4.6.BA] [Trazodone](#)

##### 4.6.BA.1] Depression

a) [Trazodone](#) is not therapeutically superior to [imipramine](#), but its side effects are less troublesome [1125] [1126][1127][1128][1129][1130]. Anticholinergic side effects occurred more frequently in patients treated with [imipramine](#) than those treated with [trazodone](#) in a multi-centre trial [1131].

b) A multicenter trial involving 379 patients treated with [trazodone](#) 200 to 600 milligrams (mg) per day [imipramine](#) 100 to 300 mg/day or placebo for 21 to 24 days demonstrated [imipramine](#) and [trazodone](#) to be of equal efficacy [1131]. Another study involving 28 patients with [endogenous depression](#) receiving an average [trazodone](#) dose of 287 mg/day or an average [imipramine](#) dose of 140 mg/day for 28 days also demonstrated equal effectiveness between the 2 drugs [1125]. The results of a double-blind study involving 45 patients suggested that [trazodone](#) 200 to 600 mg/day produced a more rapid and prolonged improvement than did [imipramine](#) 100 to 300 mg/day [1126]. In a double-blind controlled study of 40 patients with [endogenous depression](#), [imipramine](#) (maximum daily dose 300 mg) produced more improvement of Hamilton depression scale scores on days 14 and 28 than [trazodone](#) (maximum daily dose 600 mg) [1128].

c) Seventy-four patients were enrolled in a nonrandomized study with placebo baseline treatment to evaluate the efficacy of [imipramine](#), [alprazolam](#), and [trazodone](#) in the treatment of [agoraphobia](#) [1132]. Twenty-nine patients were assigned to [imipramine](#), 28 to [trazodone](#), and 26 to [alprazolam](#) treatment. All

patients were treated with placebo for 3 weeks and then blindly switched to active treatment for clinical response and side effects. Both [imipramine](#) and [alprazolam](#) were effective in controlling the [agoraphobia](#), however, [alprazolam](#) had a faster onset of action. Clinical responses were observed within one week with [alprazolam](#) therapy and were generally not observed in [imipramine](#) treated patients until the third or fourth week of therapy. [Trazodone](#) therapy was considered not effective in the treatment of [agoraphobia](#).

d) In a double-blind controlled study, [imipramine](#) and placebo were compared with [trazodone](#) in the treatment of 45 hostile patients with primary depression. The mean doses received during this study were 6.26 capsules/day of 50 milligrams (mg) [trazodone](#), 6.37 capsules/day of [imipramine](#) 25 mg or 10.67 capsules/day of placebo. Three of 17 patients in the [trazodone](#) groups experienced a 50% reduction in the Hamilton total score on or before day 7 of therapy. On day 14, 8 patients from the [trazodone](#) group achieved this level of improvement. Of the [imipramine](#)-treated patients, no one in the group showed a 50% improvement at day 7. However, by day 14, eight patients in the group had also experienced at least a 50% reduction in total Hamilton differences in the subjects tested through the structured clinical interview. Clinical global impressions showed a highly significant difference between [trazodone](#) and placebo in the proportion of improved patients at the end of 28 days of treatment. Global ward behavior indicated that [trazodone](#) was significantly ( $p$  less than 0.01) better than placebo for tense, anxious, inwardly distressed behavior and difficulty in sleeping. It was significantly ( $p$  less than 0.05) better for tired, worn out and lacking energy behavior and anxious, worried, afraid behavior and concern for bodily health. [Trazodone](#) was slightly better ( $p$  less than 0.10) for irritable, annoyed, impatient or angry behavior. Drowsiness was the most frequent side effect experienced by [trazodone](#) treated patients. Anticholinergic effects were the most common effects in the [imipramine](#) group [1126].

e) Ten institutions participated in a multi-center, double-blind, placebo-controlled evaluation of either [trazodone](#) or [imipramine](#) in 263 in-patients. Inclusion criteria included primary depression of the endogenous type, minimum score of 18 on the Hamilton Rating Scale for depression (HAM-D) and at least 7 of 21 symptoms in 3 of 5 categories of the symptom profile for depression. Initial doses were 200 mg and 100 mg daily for [trazodone](#) or [imipramine](#). At the end of 28 days, 113 patients dropped out due to lack of efficacy or side effects. Drop out rates were 37% each for [imipramine](#) and [trazodone](#) and 58% for placebo. Both drugs were statistically superior to placebo in improvement of HAM-D and clinical global interview. There was no significant difference between [trazodone](#) and [imipramine](#). Both [trazodone](#) and placebo caused statistically significantly fewer anticholinergic side effects, 19% and 14% compared WITH [imipramine](#) 52% [1133].

#### 4.6.BB] Trimipramine

##### 4.6.BB.1] Depression

a) One study showed [trimipramine](#) to be slightly superior to [imipramine](#). Thirty-nine inpatients with [endogenous depression](#) received either [imipramine](#) or [trimipramine](#) increased over 14 days to a maximum of 300 milligrams at bedtime and continued another 2 weeks. There were fewer adverse reactions (tremor, drowsiness, insomnia and dry mouth) than with [trimipramine](#); however, nasal congestion occurred more frequently during [trimipramine](#) therapy [1099].

b) [Imipramine](#) was compared with [trimipramine](#) in 44 patients with [psychotic depression](#) (average duration of illness over 1 year) [1100]. [Trimipramine](#) was administered in doses of 25 mg three times daily for 1 week followed by 50 mg three times daily for 2 more weeks. Overall recovery was reported in 18 patients receiving [trimipramine](#) (in 8.7 days) compared with 10 patients receiving [imipramine](#) (8.9 days). In addition, anxiety and insomnia responded much better in patients receiving [trimipramine](#). Similar results have been reported by others [1101].

#### 4.6.BC] Tryptophan

**4.6.BC.1] Depression**

a) L-tryptophan 6 grams and imipramine 150 milligrams/day were effective in relieving endogenous and non-endogenous depression in 59 patients. Imipramine improved agitation, while L-tryptophan improved work and activities in patients with endogenous depression. Imipramine therapy improved suicidal feelings in patients with non-endogenous depression (Lindberg et al, 1979).

**4.6.BD] Venlafaxine****4.6.BD.1] Depression**

a) Venlafaxine and imipramine resulted in similar improvement in depression with melancholia in hospitalized patients at 6 weeks; however, venlafaxine produced an earlier response than imipramine on 1 test [1147]. Over 5 days, the dose of venlafaxine was rapidly increased from 75 to 375 milligrams(mg)/day; this dose was continued until day 14 and was then decreased to 150 mg/day. The dose of imipramine was increased from 50 to 200 mg/day over 5 days and was continued at this dose for the remainder of the study. The time to a 50% response rate was similar for the Montgomery-Asberg Depression Rating Scale (MADRS), but for the 21-item Hamilton Rating Scale for Depression (HAM-D), the time to response was 1 week earlier with venlafaxine than imipramine ( $p=0.036$ ). Adverse effects were reported in 69% and 76% of patients treated with venlafaxine and imipramine, respectively. Statistically significant differences in dry mouth and tremor were reported for imipramine ( $p$  less than 0.05) and nausea for venlafaxine ( $p=0.011$ ). While this study enrolled 167 patients, this was lower than planned, and only 115 patients completed the 6-week study. Additional studies are needed to provide conclusive evidence for a more rapid onset of effect with venlafaxine.

b) Venlafaxine was found to have antidepressant efficacy comparable to imipramine in outpatients with moderate to marked depression. Venlafaxine was compared to imipramine in a 6 week, double-blind placebo controlled study in 224 outpatients with depression of moderate to marked severity. Baseline and weekly efficacy measurements were obtained utilizing the 21 item Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impression severity and improvement scales (CGI). The mean maximal total daily dose of venlafaxine was 182 mg +/- 48 milligrams and the mean maximal total daily dose of imipramine was 176 milligrams and +/- 56 mg. All study medications were administered in a three times a day schedule after meals. Venlafaxine showed a significant clinical advantage over imipramine at the week 6 endpoint on the Ham-D total score. It was noted that this effect was probably due to the higher attrition rate for imipramine as compared to venlafaxine. Attrition rates due to adverse effects were 25% and 16% for imipramine and venlafaxine respectively. Nausea, sedation, dry mouth, and dizziness were the most prominently reported adverse effects for venlafaxine [1148].

**4.6.BE] Viloxazine****4.6.BE.1] Depression**

a) SUMMARY: Several controlled studies have reported the equivalent efficacy of viloxazine 150 to 450 milligrams daily and imipramine 75 to 225 milligrams daily in the treatment of depression in inpatients and outpatients [1138][1139][1140][1136][1141][1142][1143]. Side effects in some of these reports, primarily anticholinergic, were less with viloxazine; however, others have indicated a similar incidence as imipramine [1140].

b) At least 2 studies have reported a similar clinical response to placebo as with viloxazine and imipramine in depressive neurosis [1144][1145]. These data do not necessarily indicate the inefficacy of viloxazine (or imipramine) in this patient group, but rather reflect the methodological problems of placebo

responsiveness in neurotic populations. Placebo effects may also explain the reported early onset of effects with viloxazine in some clinical studies, both neurotic and [endogenous depression](#).

**c)** Better scores were reported on the Hamilton Depression Scale in patients treated with viloxazine 50 milligrams three times/day compared to those treated with [imipramine](#) 25 milligrams three times/day (Elwin, 1980). The double-blind study involved 59 depressed patients. However, this data was not reproduced in 40 depressed patients treated with viloxazine 300 mg/day or [imipramine](#) 150 mg/day [1136], nor in 28 depressed patients [1138].

**d)** Viloxazine was compared with [imipramine](#) in the treatment of [endogenous depression](#) in a double-blind study involving 20 patients [1140]. Patients were randomly assigned to viloxazine 150 to 450 milligrams (mg) daily or [imipramine](#) 75 to 225 milligrams daily (10 patients in each group). [Flurazepam](#) or [chloral hydrate](#) were given for sleep as needed. Clinical global impressions indicated that 7 viloxazine patients (70%) and 7 [imipramine](#) patients (70%) improved during treatment; 2 patients receiving viloxazine and 3 receiving [imipramine](#) remained unchanged and 1 patient receiving viloxazine worsened. The Hamilton Psychiatric Rating Scale for Depression indicated improvement with both drugs with no differences between them. [Imipramine](#) had a faster onset of action for depression (1 week versus 2 weeks). The Hamilton Psychiatric Rating Scale for Anxiety also showed similar degrees of improvement, however, viloxazine had a more rapid onset (1 week versus 2 weeks). Viloxazine had no effect on improving sleep disturbances as determined by the Hamilton Depression Scale, a similar finding compared with other reports. Side effects were similar for both drugs with 1 patient in each group developing PVCs during treatment (both patients had abnormal EKGs at initiation of treatment).

**e)** Viloxazine and [imipramine](#) has similar efficacy in a 5-week study involving 49 patients with [endogenous depression](#) [1141]. Viloxazine was initiated in oral doses of 50 milligrams (mg) three times a day with meals, with the last dose being given at 5 p.m. [Imipramine](#) was given initially in doses of 25 milligrams orally three times a day in a similar fashion. The dose was increased starting in the second week of the study to a maximum of viloxazine 400 mg daily and [imipramine](#) 200 mg daily by the fourth and fifth weeks. The mean daily dosage by the fifth week of the study was 380 mg daily for viloxazine and 192 mg daily for [imipramine](#). Both drugs resulted in improvement based upon Clinical Global Impressions, the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, and the Brief Psychiatric Rating Scale. Based upon Clinical Global Impressions, 12 of 24 viloxazine patients were very much improved, with 5 much improved; 13 of 25 [imipramine](#) patients were very much improved, with 7 being much improved. Side effects occurred more frequently in [imipramine](#) patients. Anticholinergic side effects of dry mouth, constipation, blurred vision, sweating, and sedation occurred more frequently in the [imipramine](#) group. However, nausea and vomiting occurred only in viloxazine patients.

#### 4.6.BE.2] Nocturnal [enuresis](#)

**a)** Viloxazine was evaluated in the treatment of nocturnal [enuresis](#) in a controlled study with [imipramine](#) and placebo in 33 children [1146]. The drugs were randomly assigned for a 7-week period. Viloxazine 100 milligrams (mg) at bedtime was administered to children between 5 and 10 years of age. [Imipramine](#) was given in doses of 50 and 75 milligrams, respectively. At week 7, significantly more dry nights occurred with both viloxazine and [imipramine](#) as compared to placebo, with no statistically significant difference between the two active agents. Toxicity was greater in the [imipramine](#) patients, consisting of, primarily anticholinergic effects. These data suggest the efficacy of viloxazine in enuretic children. Viloxazine may prove to be a useful alternative to [imipramine](#) in children who develop side effects during [imipramine](#) therapy.

#### 4.6.BE.3]) Adverse Effects

**a)** The most frequent side effects associated with viloxazine therapy are nausea and vomiting [1135] [1136], and the incidence of anticholinergic side effects is much lower than with [imipramine](#).



b) Viloxazine appears to cause less [impairment of psychomotor](#) performance than [imipramine](#). The driving of male volunteers was tested after multiple doses of viloxazine 50 milligrams three times/day, [imipramine](#) 25 milligrams three times/day, placebo, or nothing. The group treated with [imipramine](#) demonstrated significantly worse performance in the gap acceptance test and subsidiary task responses. There was no effect on driving skills noted 2 hours after the first dose of each drug [1137].

#### 4.6.BF] Zimeldine

##### 4.6.BF.1] Agoraphobia

a) A double-blind comparison of zimeldine, [imipramine](#), and placebo in the treatment of 44 patients with [agoraphobia with panic attacks](#) revealed that zimeldine was better, (not statistically significant), than [imipramine](#) and placebo therapy [1207]. In fact, the [imipramine](#) therapy was not considered to be superior to placebo. Previous positive results with [imipramine](#) [1208][1209] would indicate that the dose of [imipramine](#) used in this study was too low (150 mmilligrams/day) or the group of patients studied is not indicative of all patients with [agoraphobia](#) and panic attacks. Until further studies are conducted the utilization of zimeldine in the treatment of [agoraphobia](#) should be limited to research studies.

##### 4.6.BF.2] Depression

a) Zimeldine 100 milligrams orally twice a day was compared with oral [imipramine](#) 50 milligrams three times a day in the treatment of primary [major depressive disorders](#) (endogenous) in 95 patients in a controlled study [1210]. During the 4-week study, zimeldine produced similar antidepressant activity as [imipramine](#) as evaluated on the Hamilton Depression Scale. Zimeldine was reported more effective in patients over the age of 40, patients whose initial onset occurred at over 40 years, patients with mild-to-moderate depression and patients who had previously failed to show an appreciable response to other antidepressants. Zimeldine was less toxic than [imipramine](#), primarily with regard to anticholinergic symptoms.

b) Zimeldine demonstrated significantly lower Hamilton Depression scale total scores compared with [imipramine](#). One hundred forty depressed patients were administered zimeldine, [imipramine](#), and matching placebo in doses of 50 milligrams twice a day. Fewer adverse effects were reported in the zimeldine group [1211].

##### 4.6.BF.3] Adverse Effects

a) Zimeldine did not differ in psychomotor or cognitive function tests in 18 healthy volunteers. In a double-blind, randomized fashion, each subject received zimeldine 100 milligrams, [imipramine](#) 50 milligrams, or matching placebo. A battery of tests did not exhibit a significant difference between active drugs [1205].

b) Zimeldine in therapeutic doses (200 milligrams/day) produces more pronounced anticholinergic effects, as measured by accommodation width and salivary secretion rate, than [imipramine](#) in therapeutic doses (75 milligrams/day) [1206].

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