

DRUGDEX-EV 2756

MICROMEDEX

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**DEXTROAMPHETAMINE/AMPHETAMINE**

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**0.0] Overview**

**1] Class**

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

CNS Stimulant

**2] Dosing Information**

**a) Adult**

**1) [Attention deficit hyperactivity disorder](#)**

**a)** extended-release, 20 mg ORALLY daily [1]

**2) [Narcolepsy](#)**

**a)** immediate-release, 5 to 60 mg/day ORALLY in divided doses [2]

**b) [Pediatric](#)**

**1)** (immediate-release) not FDA approved in children under 3 years of age with attention deficit hyperactivity disorder [2]

**2)** (extended-release) not FDA approved in children under 6 years of age with attention deficit hyperactivity disorder [1]

**a) [Attention deficit hyperactivity disorder](#)**

**1)** immediate release (age 3 to 5 yr), initial 2.5 mg ORALLY every morning; may increase daily dose in 2.5 mg increments at weekly intervals until optimal response [2]

**2)** immediate release (age 6 yr and older), initial 5 mg ORALLY once or twice daily; may increase daily dose in 5 mg increments at weekly intervals until optimal response;

give first dose in the morning and subsequent doses at 4 to 6 hour intervals; MAX 40 mg/day [2]

**3))** extended release (6 to 12 yr), initial 10 mg ORALLY every morning (alternatively, 5 mg/day if appropriate); may increase daily dose in 5 to 10 mg increments at weekly intervals until optimal response; MAX 30 mg/day [1]

**4))** extended release (13 to 17 yr), initial 10 mg ORALLY every morning; may increase to 20 mg/day after 1 week [1]

**b)) Narcolepsy**

**1))** immediate release (age 6 to 12 yr) initial, 5 mg ORALLY once daily; may increase daily dose in 5 mg increments at weekly intervals until optimal response [2]

**2))** immediate release (age 12 yr and older) initial, 10 mg ORALLY once daily; may increase daily dose in 10 mg increments at weekly intervals until optimal response [2]

**3)) Contraindications**

**a))** Advanced [arteriosclerosis](#) [7] [8]

**b))** Agitated states [7] [8] [9]

**c))** Concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; [hypertensive crisis](#) may result [7] [8]

**d))** [Glaucoma](#) [7] [8]

**e))** History of drug abuse [7] [8]

**f))** Hypersensitivity or idiosyncrasy to sympathomimetic amines [7] [8]

**g))** [Hyperthyroidism](#) [7] [8]

**h))** Moderate to severe [hypertension](#) [7] [8]

**i))** Symptomatic [cardiovascular disease](#) [7] [8]

**4)) Serious Adverse Effects**

**a))** [Cardiomyopathy](#)

**b))** Cerebrovascular accident

**c))** [Hypersensitivity reaction](#)

**d))** [Myocardial infarction](#)

**e))** [Peripheral vascular disease](#)

**f))** [Psychotic disorder](#)

**g))** [Raynaud's disease](#)

h)) Seizure

i)) [Stevens-Johnson syndrome](#)

j)) Sudden cardiac death

k)) [Toxic epidermal necrolysis](#)

5)) Clinical Applications

a)) FDA Approved Indications

1)) [Attention deficit hyperactivity disorder](#)

2)) [Narcolepsy](#)

1.0) Dosing Information

[Drug Properties](#)

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1.1) Drug Properties

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

B)) Physicochemical Properties

1)) pKa

a)) [amphetamine](#), 9.9 [19] [10]

1.2) Storage and Stability

A)) Preparation

1)) Oral

a)) Give first dose (immediate-release) on awakening, and additional doses at 4 to 6-hour intervals. Avoid late evening doses due to resulting insomnia [2] [6].

b)) Extended-release capsules may be swallowed whole with or without food. The entire capsule contents may be sprinkled on applesauce and consumed immediately; the applesauce with sprinkled beads should be consumed in its entirety without chewing. Do not divide the dose of a single capsule [6].

B)) Oral route

1)) Capsule, Extended Release

a)) Store at a controlled room temperature of 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [19].

2)) Tablet

- a)) Store at a controlled room temperature of 20 to 25 degrees C (68 to 77 degrees F) [10].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Oral route

1.3.1.A.1] [Attention deficit hyperactivity disorder](#)

a)) Extended-Release

- 1)) The recommended initial dose for patients with [attention deficit hyperactivity disorder](#) is 20 milligrams orally per day [1].

1.3.1.A.2] [Narcolepsy](#)

- a)) The recommended dose of immediate-release tablets is 5 to 60 milligrams/day ORALLY in divided doses [2].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Oral route

1.4.1.A.1] [Attention deficit hyperactivity disorder](#)

a)) Immediate-Release

- 1)) For children aged 3 to 5 years, the recommended initial dose of immediate-release tablets is 2.5 milligrams (mg) orally every morning. Dose may be increased in 2.5-mg increments at weekly intervals until optimal response [2].

- 2)) For children aged 6 years and older, the recommended initial dose of immediate-release is 5 milligrams (mg) orally once or twice daily; with dose increase in 5-mg increments at weekly intervals until optimal response, up to 40 mg/day. Give first dose in the morning and subsequent doses at 4 to 6 hour intervals [2].

b)) Extended-Release

- 1)) For children 6 years of age and older, the starting dose of extended-release [dextroamphetamine/amphetamine](#) is 10 milligrams (mg) once daily in the morning. Doses may be increased by 10 mg at weekly intervals to a MAXIMUM dose of 30 mg/day taken once daily [1].

- 2)) For patients using immediate-release tablets, they should be switched to the same total daily dose of extended-release product and should be taken once daily in the morning [5].

1.4.1.A.2] [Narcolepsy](#)

a)) Immediate-Release

1J) For children aged 6 to 12 years, the recommended initial dose of immediate-release tablets is 5 milligrams (mg) ORALLY once daily. Dose may be increased in 5-mg increments at weekly intervals until optimal response [2].

2J) For children aged 12 years and older, the recommended initial dose of immediate-release tablet is 10 milligrams (mg) ORALLY once daily; with dose increase in 10-mg increments at weekly intervals until optimal response. Take first dose on awakening and additional doses at 4 to 6 hour intervals [2].

## 2.0J Pharmacokinetics

### Drug Concentration Levels

#### ADME

### 2.2J Drug Concentration Levels

#### AJ) Peak Concentration

1J) Linear pharmacokinetics have been demonstrated for [dextroamphetamine/amphetamine](#) in the dose range of 20 to 60 mg in adults and adolescents who weigh greater than 75 kg, in the dose range of 10 to 40 mg in adolescents weighing 75 kg or less, and in the dose range of 5 to 30 mg in children ages 6 to 12 years of age [227].

2J) Similar plasma concentration profiles of both d-amphetamine and l-amphetamine have been observed following single dose oral administration of either extended-release [dextroamphetamine/amphetamine](#) 20 mg or immediate-release [dextroamphetamine/amphetamine](#) 10 mg twice a day (separated by 4 hours) [227].

#### aJ) Age

1J) In pharmacokinetic studies, for a given dose of extended-release dextroamphetamine/amphetamine, pediatric patients demonstrated greater systemic exposure to amphetamine (higher AUC and C<sub>max</sub>) compared with adult patients. However, this was attributed primarily to the children being of lighter body weight than the adults who participated, and thus receiving a greater mg/kg dose with the fixed-dose design. When the dose was adjusted to body weight, on a mg/kg basis children demonstrated 30% lower systemic exposure compared with adults (due to faster elimination rate in children) [227].

#### bJ) Gender

1J) In a pharmacokinetic study of extended-release dextroamphetamine/amphetamine in 20 men and 20 women, females had 20-30% greater systemic exposure to amphetamine (higher AUC and C<sub>max</sub>) compared with men. However, this was attributed primarily to the women being of lighter body weight than the men who participated, and thus receiving a greater mg/kg dose with the fixed-dose design. When the dose was adjusted for body weight, on a mg/kg basis women and men demonstrated similar systemic amphetamine exposure [227].

#### BJ) Time to Peak Concentration

##### 1J) Immediate-release

aJ) 3 hours [227]

1J) Following oral administration of immediate-release dextroamphetamine/amphetamine, T<sub>max</sub> for both d-amphetamine and l-amphetamine levels occurred approximately at 3 hours [227].

2J) Extended-release

aJ) 7 hours [227]

1J) Following oral administration of extended-release dextroamphetamine/amphetamine, T<sub>max</sub> for both d-amphetamine and l-amphetamine levels occurred approximately at 3 hours [227].

CJ) Area Under the Curve

1J) Linear pharmacokinetics have been demonstrated for dextroamphetamine/amphetamine in the dose range of 20 to 60 mg in adults and adolescents who weigh greater than 75 kg, in the dose range of 10 to 40 mg in adolescents weighing 75 kg or less, and in the dose range of 5 to 30 mg in children ages 6 to 12 years of age [227].

2J) Similar plasma concentration profiles have been observed following single dose oral administration of either extended-release dextroamphetamine/amphetamine 20 mg or immediate-release dextroamphetamine/amphetamine 10 mg twice a day (separated by 4 hours) [227].

aJ) Age

1J) In pharmacokinetic studies, for a given dose of extended-release dextroamphetamine/amphetamine, pediatric patients demonstrated greater systemic exposure to amphetamine (higher AUC and C<sub>max</sub>) compared with adult patients. However, this was attributed primarily to the children being of lighter body weight than the adults who participated, and thus receiving a greater mg/kg dose with the fixed-dose design. When the dose was adjusted to body weight, on a mg/kg basis children demonstrated 30% lower systemic exposure compared with adults (due to faster elimination in children) [227].

bJ) Gender

1J) In a pharmacokinetic study of extended-release dextroamphetamine/amphetamine in 20 men and 20 women, females had 20% to 30% greater systemic exposure to amphetamine (higher AUC and C<sub>max</sub>) compared with men. However, this was attributed primarily to the women being of lighter body weight than the men who participated, and thus receiving a greater mg/kg dose with the fixed-dose design. When the dose was adjusted for body weight, on a mg/kg basis women and men demonstrated similar systemic amphetamine exposure [227].

2.3J ADME

2.3.1J Absorption

AJ) Effects of Food

**1j) No effect on extent of absorption [227]**

**aj)** While the extent of absorption is not affected by administration with food, the T<sub>max</sub> is delayed by approximately 2.5 hours when [dextroamphetamine/amphetamine](#) is administered after a high-fat meal compared with administration in the fasted state [227].

**bj)** Administration by sprinkling the capsule contents over applesauce appears to have similar absorption characteristics when compared with administering the intact capsule in the fasted state [227].

**2.3.3] Metabolism****Aj) Metabolism Sites and Kinetics****1j) Liver: variable [227]**

**aj)** [Amphetamines](#) are metabolized in the liver via oxidation. The extent to which an administered dose is hepatically metabolized is determined, in part, by the amount not excreted via the kidneys (which varies with urine pH and urine flow rate). Although multiple enzymes may be involved with oxidation of [amphetamines](#), CYP2D6 has been identified in the formation of a major active metabolite, 4-hydroxy-amphetamine. [Amphetamines](#) inhibit monoamine oxidase [227].

**Bj) Metabolites****1j) 4-hydroxy-amphetamine: active [227]**

**aj)** [Amphetamine](#) undergoes oxidation to the active metabolite, 4-hydroxy-amphetamine, which is subsequently oxidized to 4-hydroxy-norephedrine. Although there may be multiple enzymes responsible, CYP2D6 has been identified in creating 4-hydroxy-amphetamine [227].

**2j) norephedrine: active [227]**

**aj)** [Amphetamine](#) undergoes oxidation to the active metabolite, norephedrine, which is subsequently oxidized to 4-hydroxy-norephedrine [227].

**2.3.4] Excretion****Aj) Kidney****1j) Renal Excretion (%)**

**aj)** 30% to 40%, unchanged; 50% changed [227]

**1j)** The excretion of unchanged amphetamine is dependent on urinary pH and urine flow rate. At normal urine pH, approximately 30% to 40% of unchanged drug is excreted in the urine, with 50% recovered as derivatives of alpha-hydroxy-amphetamine. At an alkaline urinary pH, a smaller proportion of amphetamine is in the ionized form, thus renal excretion decreases and hepatic metabolism increases. When urine pH is acidic or urine flow rate is high, a greater proportion of an

administered amphetamine dose is renally excreted. Depending upon urine pH, observed urinary recovery of amphetamine may range from 1% to 75% [227].

### **2.3.5] Elimination Half-life**

#### **A)] Parent Compound**

##### **1)] Adults**

###### **a)] 10 to 13 hours [227]**

**1)]** The mean elimination half-lives for d-amphetamine and l-amphetamine in adults are 10 and 13 hours, respectively [227].

##### **2)] Adolescents**

###### **a)] 11 to 14 hours [227]**

**1)]** The mean elimination half-lives for d-amphetamine and l-amphetamine are 11 and 13 to 14 hours, respectively, in adolescents 13 to 17 years old who weigh 75 kg or less [227].

##### **3)] Children 6 to 12 years old**

###### **a)] 9 to 11 hours [227]**

**1)]** The mean elimination half-lives for d-amphetamine and l-amphetamine in children 6 to 12 years of age are 9 and 11 hours, respectively [227].

### **3.0] Cautions**

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

#### **3.0.A] Black Box WARNING**

##### **Oral (Tablet; Capsule, Extended Release)**

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence. Pay particular attention to the possibility of subjects obtaining amphetamines for non-therapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly.

Misuse of amphetamine may cause sudden death and serious cardiovascular adverse reactions [7] [8].



### 3.1] Contraindications

- A) Advanced [arteriosclerosis](#) [7] [8]
- B) Agitated states [7] [8] [9]
- C) Concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; [hypertensive crisis](#) may result [7] [8]
- D) [Glaucoma](#) [7] [8]
- E) History of drug abuse [7] [8]
- F) Hypersensitivity or idiosyncrasy to sympathomimetic amines [7] [8]
- G) [Hyperthyroidism](#) [7] [8]
- H) Moderate to severe [hypertension](#) [7] [8]
- I) Symptomatic [cardiovascular disease](#) [7] [8]

### 3.2] Precautions

- A) Black Box Warning:
- B) -- Abuse and dependence may occur; assess risk prior to initiation and monitoring recommended during therapy [7] [8]
- C) -- Administration of [amphetamines](#) for prolonged periods should be avoided as this may lead to drug dependence [7]
- D) -- [Amphetamine](#) misuse; may cause sudden death and serious cardiovascular events [7] [8]
- E) Cardiovascular:
- F) -- Sudden death has been reported with CNS stimulant treatment in patients with structural cardiac abnormalities or serious cardiac problems, including [cardiomyopathy](#), [coronary artery disease](#), and serious heart rhythm abnormalities; avoid use [7] [8]
- G) -- Blood pressure and heart rate increases have been reported and may impact underlying medical conditions such as preexisting [hypertension](#), [heart failure](#), recent [myocardial infarction](#), ventricular [arrhythmia](#); monitoring recommended [7] [8]
- H) -- [Myocardial infarction](#), [stroke](#), and death have been reported with stimulant treatment at usual doses in adults; avoid use in patient with structural cardiac abnormalities or serious cardiac problems, including [cardiomyopathy](#), [coronary artery disease](#), and serious heart rhythm abnormalities [7] [8]
- I) -- Peripheral vasculopathy (eg, [Raynaud's phenomenon](#)) has been reported and may result in digital [ulceration](#) and/or soft tissue breakdown; monitoring recommended; dosage adjustment or discontinuation may be necessary [7] [8]
- J) Endocrine and Metabolic:
- K) -- Growth suppression may occur with consistent use; monitoring recommended and treatment interruption may be necessary [7] [8]
- L) Neurologic:
- M) -- Seizures may occur due to a lowering of the convulsive threshold, particularly in patients with seizure history or EEG abnormalities; discontinue [7] [8]
- N) -- History of motor and phonic tics; risk of exacerbation [7] [8]
- O) -- History of [Tourette syndrome](#); risk of exacerbation [7] [8]
- P) Ophthalmic:
- Q) -- Visual disturbances, including difficulties with accommodation and blurring of vision, have been reported [7] [8]
- R) Psychiatric:
- S) -- Aggressive behavior and hostility have been reported; monitoring recommended [7] [8]
- T) -- [Bipolar disorder](#); may precipitate a mixed/[manic episode](#) [7] [8]

U) -- Pre-existing [psychosis](#); treatment may exacerbate symptoms of behavior disturbance and thought disorder [7] [8]

V) -- Psychotic or manic symptoms (eg, hallucinations, delusional thinking, or mania) may occur in children or adolescents with no prior history of psychotic illness at usual doses; discontinuation may be necessary [7] [8]

W) Concomitant use:

X) --Avoid use of gastrointestinal alkalizing agents (eg, antacids) [7]

### 3.3] Adverse Reactions

#### 3.3.1] Cardiovascular Effects

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

1) [Cardiomyopathy](#) has been associated with chronic [amphetamine](#) use. Patients with serious structural or other cardiac abnormalities (eg, [cardiomyopathy](#), heart rhythm abnormalities, [coronary artery disease](#)) should generally not be treated with stimulant medications. Conduct a thorough cardiac history (including family history of sudden death or [ventricular arrhythmia](#)) and physical exam before treatment initiation. Patients should be monitored for larger blood pressure or heart rate increases. A cardiac evaluation (eg, ECG, [echocardiogram](#)) should be performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms indicative of cardiac disease [10] [8] .

##### 3.3.1.B] Increased systolic arterial pressure

###### 1) Summary

a) An average elevation in blood pressure of 2 to 4 mmHg is associated with stimulant medications. Use with caution in patients with cardiac conditions which may be exacerbated by further blood pressure increases (eg, preexisting [hypertension](#), [heart failure](#), recent [myocardial infarction](#), [ventricular arrhythmia](#)). Conduct a thorough cardiac history (including family history of sudden death or [ventricular arrhythmia](#)) and physical exam before treatment initiation. Patients should be monitored for larger blood pressure or heart rate increases. A cardiac evaluation (eg, ECG, [echocardiogram](#)) should be performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms indicative of cardiac disease [10] [8].

2) Incidence: extended-release: pediatrics, 7% to 35% [8]

###### 3) Pediatrics

a) Isolated elevations in systolic blood pressure (15 mmHg or more) were observed in 7% of patients receiving Adderall XR(R) 10 or 20 mg (n=100) compared with 11% of placebo-treated patients (n=64) during a 4-week, controlled study in adolescents with ADHD. Isolated diastolic blood pressure elevations (8 mmHg or more) were observed in 22% of patients in the Adderall XR(R) treatment group compared with 25% of placebo-treated patients [8].

b) A single-dose [pharmacokinetic study](#) in 23 adolescents showed isolated increases in systolic blood pressure (above the upper 95% CI for age, gender, and stature) in 12% of patients treated with Adderall XR(R) 10 mg and 35% of patients treated with Adderall XR(R) 20 mg. All increases were transient, appeared maximal at 2 to 4 hours post dose, and were not associated with symptoms [8].

##### 3.3.1.C] [Myocardial infarction](#)

###### 1) Adults

a) **Myocardial infarction** has been reported in adults treated with stimulant therapy at usual doses for ADHD. Adults with serious structural or other cardiac abnormalities (eg, **cardiomyopathy**, heart rhythm abnormalities, **coronary artery disease**) should generally not be treated with stimulant medications. Conduct a thorough cardiac history (including family history of sudden death or **ventricular arrhythmia**) and physical exam before treatment initiation. Patients should be monitored for larger blood pressure or heart rate increases. A cardiac evaluation (eg, ECG, **echocardiogram**) should be performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms indicative of cardiac disease [10] [8].

b) In a retrospective cohort study of 443,198 adults aged 25 to 64 years (mean age 42 years), a slightly reduced risk in the combined primary endpoint of serious cardiovascular events (sudden cardiac death (SCD), acute **myocardial infarction** (MI), and **stroke**) was observed in those persons currently receiving an ADHD medication compared with nonusers of ADHD medications (adjusted relative risk, 0.83; 95% CI, 0.72 to 0.96). Electronic health records at 4 sites supplied the data for the study populations. Users of ADHD medications (n=150,359; **methylphenidate**, 45%; **amphetamines**, 44%; **atomoxetine**, 8%; or **pemoline**, 4%) were matched in a 2:1 ratio with persons who had no record of ADHD medication use in the 365 days prior to cohort entry (n=292,839). Each user was matched with 2 nonusers by study site, birth year, sex, and calendar year. A total of 1357 cases of MI, 296 cases of SCD, and 575 cases of **stroke** occurred during the 806,182 person-years of follow-up (median 1.3 years per person) [11].

## 2) Pediatrics

a) In a retrospective cohort study involving 1,200,438 children and young adults aged 2 to 24 years (mean age 11.1 years) and 2,579,104 person-years of follow-up (373,667 person-years of current use of ADHD drugs), there was no significant difference in the combined primary endpoint of serious cardiovascular events (sudden cardiac death, acute **myocardial infarction**, and **stroke**) in those who received an ADHD drug (**methylphenidate**, **dexmethylphenidate**, **dextroamphetamine**, **amphetamine** salts, **atomoxetine**, or **pemoline**) compared with those who did not (adjusted hazard ratio, 0.75; 95% CI, 0.31 to 1.85) [12]. Although this study found no association between the use of ADHD drugs and serious cardiovascular events, the possibility of a small to modest increase in risk cannot be excluded because of the small number of serious cardiovascular events in the patients studied [13]. Conduct a thorough cardiac history (including family history of sudden death or **ventricular arrhythmia**) and physical exam before treatment initiation. Patients should be monitored for larger blood pressure or heart rate increases. A cardiac evaluation (eg, **electrocardiogram**, **echocardiogram**) should be performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms indicative of cardiac disease [10] [8].

### 3.3.1.D) Palpitations

1) Incidence: extended-release: adults, 2% to 4% [8]

2) Palpitations have been reported during therapy [10] and in postmarketing surveillance [8]. Palpitation was reported in 2% to 4% of patients administered Adderall XR(R) 20, 40, or 60 mg/day (n=191) and more frequently than in patients in the placebo group (n=64) during a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD [8].

### 3.3.1.E) Peripheral vascular disease

1) General Information

a) Signs and symptoms are usually mild and intermittent, but digital [ulceration](#) and soft tissue breakdown has rarely occurred. Peripheral vasculopathy including [Raynaud's phenomenon](#) has occurred at different times and in all age groups, at any point in treatment [7] [8].

**2) Prevention and Management**

a) Reducing the dose or discontinuing therapy may improve signs and symptoms. Monitor patients carefully for digital changes during treatment, and if clinically appropriate, refer patients to a rheumatologist for further clinical evaluation [7] [8].

**3) Postmarketing**

a) Peripheral vasculopathy, including [Raynaud's phenomenon](#), has been reported [7] [8].

**3.3.1.F] [Raynaud's disease](#)**

**1) General Information**

a) Signs and symptoms are usually mild and intermittent, but digital [ulceration](#) and soft tissue breakdown has rarely occurred. Peripheral vasculopathy including [Raynaud's phenomenon](#) has occurred at different times and in all age groups, at any point in treatment [7].

**2) Prevention and Management**

a) Reducing the dose or discontinuing therapy may improve signs and symptoms. Monitor patients carefully for digital changes during treatment, and if clinically appropriate, refer patients to a rheumatologist for further clinical evaluation [7].

**3) Postmarketing**

a) Peripheral vasculopathy, including [Raynaud's phenomenon](#), has been reported [7].

**3.3.1.G] Sudden cardiac death**

**1) Adults**

a) Sudden death has been reported in adults who received stimulant therapy at usual doses for ADHD, including Adderall(R) and Adderall XR(R). Adults with serious structural or other cardiac abnormalities (eg, [cardiomyopathy](#), heart rhythm abnormalities, [coronary artery disease](#)) should generally not be treated with stimulant medications. Conduct a thorough cardiac history (including family history of sudden death or [ventricular arrhythmia](#)) and physical exam before treatment initiation. A cardiac evaluation (eg, ECG, [echocardiogram](#)) should be performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms indicative of cardiac disease [10] [8].

b) In a retrospective cohort study of 443,198 adults aged 25 to 64 years (mean age 42 years), a slightly reduced risk in the combined primary endpoint of serious cardiovascular events (sudden cardiac death (SCD), acute [myocardial infarction](#) (MI), and [stroke](#)) was observed in those persons currently receiving an ADHD medication compared with nonusers of ADHD medications (adjusted relative risk, 0.83; 95% confidence interval (CI), 0.72 to 0.96). Electronic health records at 4 sites supplied the data for the study populations. Users of ADHD medications (n=150,359; [methylphenidate](#), 45%; [amphetamines](#), 44%; [atomoxetine](#), 8%; or [pemoline](#), 4%) were matched in a 2:1 ratio with persons who had no record of ADHD medication use in the 365 days prior to cohort entry (n=292,839). Each user was matched with 2 nonusers by study site, birth year, sex and calendar year. A total of 1357 cases of MI, 296 cases of SCD, and 575 cases of [stroke](#) occurred during the 806,182 person-years of follow-up (median 1.3 years per person) [11].

## 2) Pediatrics

**a)** Sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious heart problems treated with stimulant medications at usual doses, including Adderall(R) and Adderall XR(R). Children or adolescents with serious structural or other cardiac abnormalities (eg, [cardiomyopathy](#), heart rhythm abnormalities) should generally not be treated with stimulant medications. Conduct a thorough cardiac history (including family history of sudden death or [ventricular arrhythmia](#)) and physical exam before treatment initiation. Patients should be monitored for larger blood pressure or heart rate increases. A cardiac evaluation (eg, ECG, [echocardiogram](#)) should be performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms indicative of cardiac disease [10] [8].

**b)** In a retrospective cohort study involving 1,200,438 children and young adults aged 2 to 24 years (mean age 11.1 years) and 2,579,104 person-years of follow-up (373,667 person-years of current use of ADHD drugs), there was no significant difference in the combined primary endpoint of serious cardiovascular events (sudden cardiac death, acute [myocardial infarction](#), and [stroke](#)) in those who received an ADHD drug ([methylphenidate](#), [dexmethylphenidate](#), [dextroamphetamine](#), [amphetamine](#) salts, [atomoxetine](#), or [pemoline](#)) compared with those who did not (adjusted hazard ratio, 0.75; 95% CI, 0.31 to 1.85) [12]. Although this study found no association between the use of ADHD drugs and serious cardiovascular events, the possibility of a small to modest increase in risk cannot be excluded because of the small number of serious cardiovascular events in the patients studied [13].

**c)** A retrospective, case-controlled study examined the association between stimulant medication, including [amphetamine/dextroamphetamine](#) combination drugs, and unexplained sudden death in healthy children and adolescents. In a collection of data from state vital statistics and surveys across the United States, 564 cases of sudden death in children and adolescents between the ages of 7 to 19 years were matched and compared with 564 youths who died as passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youth who experienced sudden unexplained deaths were taking stimulant medication compared with only 0.4% (n=2) of youths in the motor vehicle accident group (odds ratio (OR), 7.4; 95% CI, 1.4 to 74.9; p=0.02). Limitations to this study included the time lag between the youths' stimulant medication use and when the data was collected, family recall of information regarding clinical diagnoses, inconsistent postmortem inquiry, and the exclusion of deaths in youth with heart conditions. The authors stated that this finding should be considered when evaluating the overall risk and benefit of stimulant medication use in children and adolescents [14].

### 3.3.1.H] Tachycardia

#### 1) Summary

**a)** Average heart rate increases of 3 to 6 bpm have been reported with stimulant medications, including Adderall(R) and Adderall XR(R). Use with caution in patients with cardiac conditions which may be exacerbated by heart rate increases (eg, preexisting [hypertension](#), [heart failure](#), recent [myocardial infarction](#), [ventricular arrhythmia](#)). Conduct a thorough cardiac history (including family history of sudden death or [ventricular arrhythmia](#)) and physical exam before treatment initiation. Patients should be monitored for larger blood pressure or heart rate increases. A cardiac evaluation (eg, ECG, [echocardiogram](#)) should be performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms indicative of cardiac disease. Adults with serious structural cardiac abnormalities, [cardiomyopathy](#), serious heart rhythm

abnormalities, [coronary artery disease](#), or other serious cardiac disorders should generally not receive stimulants [10] [8].

2) Incidence: extended-release: adults, 6% [8]

3) [Tachycardia](#) occurred in 6% of patients receiving Adderall XR(R) 20, 40, or 60 mg/day (n=191) compared with 3% of patients in the placebo group (n=64) in a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD. [Tachycardia](#) was the primary reason for study discontinuation in 1.6% of patients administered Adderall XR(R) [8].

### 3.3.2] Dermatologic Effects

#### 3.3.2.A] [Alopecia](#)

1) [Alopecia](#) has been reported with the use of Adderall(R) or Adderall XR(R) [10] [8].

#### 3.3.2.B] Rash

1) Rash has been reported with the use of Adderall(R) [10].

#### 3.3.2.C] [Stevens-Johnson syndrome](#)

1) Serious skin rashes, including [Stevens-Johnson syndrome](#) and [toxic epidermal necrolysis](#), have been reported with the use of Adderall(R) [10].

#### 3.3.2.D] [Toxic epidermal necrolysis](#)

1) Serious skin rashes, including [toxic epidermal necrolysis](#) and [Stevens-Johnson syndrome](#), have been reported with the use of Adderall(R) [10].

### 3.3.3] Endocrine/Metabolic Effects

#### 3.3.3.A] Decreased body growth

1) Although not studied in patients receiving [amphetamines](#), in controlled studies of up to 36 months' duration that tracked the heights and weights of children up to age 13, long-term growth suppression was seen with consistent [methylphenidate](#) medication (ie, treatment 7 days a week year-round). On average, heights and weights were reduced by about 2 cm and 2.7 kg, respectively, over 3 years in treated children compared with untreated children. It is expected that [amphetamines](#) may cause a similar suppression of growth [10]. Monitor growth during stimulant treatment. Consider treatment interruption in patients who are not growing or gaining weight as expected [10] [8].

#### 3.3.3.B] Weight loss

1) Incidence: extended-release: adults, 10%; pediatrics, 4% to 9% [8]

2) Adults

a) Weight loss has been reported with the use of Adderall(R) and Adderall XR(R) [10] [8].

b) Weight loss was reported in 10% of patients receiving Adderall XR(R) 20, 40, or 60 mg/day (n=191) compared with 0% of patients in the placebo group (n=64) during a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD [8].

3) Pediatrics

a) Weight loss was reported in 4% of patients receiving Adderall XR(R) 10, 20, or 30 mg/day (n=374) compared with 0% of patients in the placebo group (n=210) during a randomized,



double-blind, placebo-controlled, parallel-group study conducted in children (aged 6 to 12 years) with ADHD. Weight loss was the primary reason for study discontinuation in 1.2% of children administered Adderall XR(R) in this trial [8].

**b))** Weight loss was reported in 9% of patients in the Adderall XR(R) treatment group (n=233) compared with 0% of patients in the placebo group (n=54) during a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents (aged 13 to 17 years) with ADHD [8].

### **3.3.4] Gastrointestinal Effects**

#### **3.3.4.A] Abdominal pain**

**1))** Incidence: extended-release: pediatrics, 11% to 14% [8]

**2))** Pediatrics

**a))** Abdominal pain was reported in 14% of patients receiving Adderall XR(R) 10, 20, or 30 mg/day (n=374) compared with 10% of patients in the placebo group (n=210) during a randomized, double-blind, placebo-controlled, parallel-group study conducted in children (aged 6 to 12 years) with ADHD [8].

**b))** Abdominal pain was reported in 11% of patients in the Adderall XR(R) treatment group (n=233) compared with 2% of patients in the placebo group (n=54) during a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents (aged 13 to 17 years) with ADHD [8].

#### **3.3.4.B] Loss of appetite**

**1))** Incidence: extended-release capsules: adults, 33%; pediatrics, 22% to 36% [8]

**2))** Adults

**a))** Anorexia has been reported with use of Adderall(R) and Adderall XR(R) [10] [8].

**b))** Loss of appetite was reported in 33% of patients receiving Adderall XR(R) 20, 40, or 60 mg/day (n=191) compared with 3% of patients in the placebo group (n=64) during a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD. Anorexia was the primary reason for study discontinuation in 1.6% of adults administered Adderall XR(R) in this trial [8].

**3))** Pediatrics

**a))** Loss of appetite was reported in 22% of patients receiving Adderall XR(R) 10, 20, or 30 mg/day (n=374) compared with 2% of patients in the placebo group (n=210) during a randomized, double-blind, placebo-controlled, parallel-group study conducted in children (aged 6 to 12 years) with ADHD. Anorexia was the primary reason for study discontinuation in 2.9% of children administered Adderall XR(R) in this trial [8].

**b))** Loss of appetite was a dose-related effect reported in 36% of patients in the Adderall XR(R) treatment group (n=233) compared with 2% of patients in the placebo group (n=54) during a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents (aged 13 to 17 years) with ADHD [8].

#### **3.3.4.C] Xerostomia**

1) Incidence: extended-release: adults, 35%; pediatrics, 2% to 4% [8]

2) Adults

a) Dry mouth has been reported with the use of Adderall(R) and Adderall XR(R) [10] [8].

b) Dry mouth was reported in 2% to 4% of patients administered Adderall XR(R) (n=233) and more frequently than in patients in the placebo group (n=54) during a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents aged 13 to 17 years with ADHD [8].

3) Pediatrics

a) **Aptyalism** was reported in 35% of patients receiving Adderall XR(R) 20, 40, or 60 mg/day (n=191) compared with 5% of patients in the placebo group (n=64) during a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD. Dry mouth was the primary reason for study discontinuation in 1.6% of adults administered Adderall XR(R) in this trial [8].

### 3.3.7] Immunologic Effects

#### 3.3.7.A] Hypersensitivity reaction

1) **Hypersensitivity reaction**, including **angioedema** and **anaphylaxis**, has been reported with the use of Adderall(R) [10].

### 3.3.8] Musculoskeletal Effects

#### 3.3.8.A] Rhabdomyolysis

1) Adult and Pediatric Clinical Studies

a) **Attention deficit hyperactivity disorder** (oral route): Has been reported [7]

### 3.3.9] Neurologic Effects

#### 3.3.9.A] Central nervous system stimulation, Overstimulation

1) Overstimulation has been reported with the use of Adderall(R) or Adderall XR(R) [10] [8].

#### 3.3.9.B] Cerebrovascular accident

1) Adults

a) **Stroke** has been reported in adults receiving stimulant therapy at usual doses for ADHD. Adults with serious structural or other cardiac abnormalities (eg, **cardiomyopathy**, heart rhythm abnormalities, **coronary artery disease**) should generally not be treated with stimulant medications. Conduct a thorough cardiac history (including family history of sudden death or **ventricular arrhythmia**) and physical exam before treatment initiation. Patients should be monitored for larger blood pressure or heart rate increases. A cardiac evaluation (eg, **electrocardiogram**, **echocardiogram**) should be performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms indicative of cardiac disease [10] [8].

b) In a retrospective cohort study of 443,198 adults aged 25 to 64 years (mean age 42 years), a slightly reduced risk in the combined primary endpoint of serious cardiovascular events (sudden cardiac death (SCD), acute **myocardial infarction** (MI), and **stroke**) was observed in those



persons currently receiving an ADHD medication compared with nonusers of ADHD medications (adjusted relative risk, 0.83; 95% confidence interval (CI), 0.72 to 0.96). Electronic health records at 4 sites supplied the data for the study populations. Users of ADHD medications (n=150,359; methylphenidate, 45%; amphetamines, 44%; atomoxetine, 8%; or pemoline, 4%) were matched in a 2:1 ratio with persons who had no record of ADHD medication use in the 365 days prior to cohort entry (n=292,839). Each user was matched with 2 nonusers by study site, birth year, sex and calendar year. A total of 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred during the 806,182 person-years of follow-up (median 1.3 years per person) [11].

c) Cerebrovascular accident has been associated with amphetamine use [15].

## 2) Pediatrics

a) In a retrospective cohort study involving 1,200,438 children and young adults aged 2 to 24 years (mean age 11.1 years) and 2,579,104 person-years of followup (373,667 person-years of current use of ADHD drugs), there was no significant difference in the combined primary endpoint of serious cardiovascular events (sudden cardiac death, acute myocardial infarction, and stroke) in those who received an ADHD drug (methylphenidate, dextmethylphenidate, dextroamphetamine, amphetamine salts, atomoxetine, or pemoline) compared with those who did not (adjusted hazard ratio, 0.75; 95% CI, 0.31 to 1.85) [12]. Although this study found no association between the use of ADHD drugs and serious cardiovascular events, the possibility of a small to modest increase in risk cannot be excluded because of the small number of serious cardiovascular events in the patients studied [13]. Conduct a thorough cardiac history (including family history of sudden death or ventricular arrhythmia) and physical exam before treatment initiation. Patients should be monitored for larger blood pressure or heart rate increases. A cardiac evaluation (eg, electrocardiogram, echocardiogram) should be performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms indicative of cardiac disease [10] [8].

### 3.3.9.C] Dizziness

#### 1) Adult and Pediatric Clinical Trials

a) ADHD (oral route): Has been reported [7].

### 3.3.9.D] Dyskinesia

1) Dyskinesia has been reported with the use of Adderall(R) [10].

### 3.3.9.E] Gilles de la Tourette's syndrome

1) New-onset tics and exacerbation of motor tics, phonic tics, and Tourette syndrome have been reported with amphetamine treatment [8] [10]. Evaluate patients and their families for tics and Tourette syndrome before initiating therapy [10].

### 3.3.9.F] Headache

1) Incidence: extended-release: adults, 26% [8]

2) Headache has been reported in 26% of patients receiving Adderall XR 20, 40, or 60 mg/day (n=191) compared with 13% of patients in the placebo group (n=64) during a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD. Headache was the primary reason for study discontinuation in 1.6% of adults administered Adderall XR(R) in this trial [8].

### 3.3.9.G] Insomnia

**1) Summary**

**a)** Avoid administration in the late evening due to the possibility of insomnia [10].

**2)** Incidence: extended-release: adults, 27%; pediatrics, 12% to 17% [8]

**3) Adults**

**a)** Insomnia was reported in 27% of patients receiving Adderall XR(R) 20, 40, or 60 mg/day (n=191) compared with 13% of patients in the placebo group (n=64) in a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD. Insomnia was the primary reason for study discontinuation in 5.2% of patients administered Adderall XR(R) [8].

**4) Pediatrics**

**a)** Insomnia occurred in 17% of patients receiving Adderall XR(R) 10, 20, or 30 mg/day (n=374) compared with 2% of patients in the placebo group (n=210) during a randomized, double-blind, placebo-controlled, parallel-group study conducted in children (aged 6 to 12 years) with ADHD. Insomnia was the primary reason for study discontinuation in 1.5% of patients administered Adderall XR(R) [8].

**b)** Insomnia occurred in 12% of patients in the Adderall XR(R) treatment group (n=233) compared with 4% of patients in the placebo group (n=54) during a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents (aged 13 to 17 years) with ADHD [8].

**3.3.9.H) Lowered convulsive threshold**

**1)** There is some clinical evidence that stimulants may lower the convulsive threshold in patients with a prior history of seizures or prior EEG abnormalities. Rarely, seizures have developed in patients without a history of seizures and no prior EEG evidence of seizure. Discontinue therapy if seizures develop [10] [8].

**3.3.9.I) Paresthesia**

**1)** Paresthesia, including formication, has been associated with the use of [amphetamine](#), Adderall(R), or Adderall XR(R) [16].

**3.3.9.J) Seizure**

**1)** There is some clinical evidence that stimulants may lower the convulsive threshold in patients with a prior history of seizures or prior EEG abnormalities. Rarely, seizures have developed in patients without a history of seizures and no prior EEG evidence of seizure. Discontinue therapy if seizures develop [10] [8].

**3.3.9.K) Tic**

**1)** New-onset tics and exacerbation of motor tics, phonic tics, and [Tourette syndrome](#) have been reported with [amphetamine](#) treatment [8] [10]. Evaluate patients and their families for tics and [Tourette syndrome](#) before initiating therapy [10] .

**3.3.9.L) Tremor**

**1)** Tremor has been reported with the use of Adderall(R) or Adderall XR(R) [10] [8].

**3.3.10) Ophthalmic Effects****3.3.10.A) Blurred vision**

1J) Blurred vision has been reported with the use of Adderall(R) or Adderall XR(R) [10] [8].

### 3.3.10.B] **Disorder of accommodation**

1J) Accommodation difficulties have been associated with stimulant treatment [10].

### 3.3.10.C] **Mydriasis**

1J) Mydriasis has been reported with the use of Adderall(R) or Adderall XR(R) [10] [8].

## 3.3.12] **Psychiatric Effects**

### 3.3.12.A] **Aggressive behavior**

1J) Aggressive or hostile behavior has been observed in children and adolescents with ADHD. Aggression has been reported with the use of Adderall(R) or Adderall XR(R). Although there is no systematic evidence that stimulant therapy causes aggressive or hostile behavior, monitoring for new-onset or worsening aggression or hostility is recommended, especially during treatment initiation [10] [8].

### 3.3.12.B] **Depression**

1J) Depression has been reported with the use of Adderall(R) [10].

### 3.3.12.C] **Dysphoric mood**

1J) **Dysphoria** has been reported with the use of Adderall(R) or Adderall XR(R) [8] [10].

### 3.3.12.D] **Euphoria**

1J) Euphoria has been reported with the use of Adderall(R) or Adderall XR(R) [8] [10].

### 3.3.12.E] **Feeling angry**

1J) Anger has been reported with the use of Adderall(R) or Adderall XR(R) [10] [8].

### 3.3.12.F] **Feeling nervous**

1J) Incidence: extended release: adults, 13%; pediatrics, 6% [8]

#### 2J) Adults

aJ) Nervousness was reported in 13% of patients receiving Adderall XR(R) 20, 40, or 60 mg/day (n=191) compared with 13% of patients administered placebo (n=64) during a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD. Nervousness was the primary reason for study discontinuation in 1.6% of adults administered Adderall XR(R) in this trial [8].

#### 3J) Pediatrics

aJ) Nervousness was reported in 6% of patients receiving Adderall XR(R) 10, 20, or 30 mg/day (n=374) compared with 2% of patients in the placebo group (n=210) during a randomized, double-blind, placebo-controlled, parallel-group study conducted in children aged (6 to 12 years) with ADHD [8].

bJ) Nervousness was reported in 6% of pediatric patients administered Adderall XR(R) (n=233) compared with 6% of patients administered placebo (n=54) during a randomized, double-blind,

placebo-controlled, multicenter, parallel-group study conducted in adolescents (aged 13 to 17 years) with ADHD [8].

### 3.3.12.G| Hostile behavior

1) Aggressive or hostile behavior has been observed in children and adolescents with ADHD. Although there is no systematic evidence that stimulant therapy causes aggressive or hostile behavior, monitoring for new-onset or worsening aggression or hostility is recommended, especially during treatment initiation [10] [8].

### 3.3.12.H| Irritability

1) Irritability has been reported with the use of Adderall(R) or Adderall XR(R) [8] [8].

### 3.3.12.I| Mania

#### 1) Summary

a) Stimulants may induce mixed/[manic episodes](#) in patients with comorbid [bipolar disorders](#) and exacerbate symptoms of behavior disturbance or thought disorder in patients with a comorbid [psychotic disorder](#). Exercise caution when using stimulants in these patients. Baseline screening should include a detailed psychiatric history (including family history of depression, [bipolar disorder](#), or suicide) [10] [8].

#### 2) Pediatrics

a) Stimulants may cause treatment-emergent psychotic or manic symptoms (eg, hallucinations, delusional thinking, mania) at recommended doses in children and adolescents without a history of mania or psychotic illness [10] [8]. In pooled analyses of multiple short-term clinical studies, new psychotic or manic symptoms occurred in 0.1% of patients treated for several weeks with [methylphenidate](#) or [amphetamine](#) at usual doses (n=3482) compared with 0% of placebo-treated patients. Consider treatment discontinuation if symptoms occur [10].

b) In a review of 49 randomized, controlled, clinical pediatric ADHD trials involving psychostimulant medications ([atomoxetine](#) hydrochloride, [methylphenidate](#) hydrochloride, [modafinil](#), and [dexmethylphenidate](#) hydrochloride), the rate of [psychosis](#)/mania events in subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of [psychosis](#) or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of [psychosis](#) or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications ([methylphenidate](#) hydrochloride, [atomoxetine](#) hydrochloride, and mixed salts of a single entity [amphetamine](#) product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset [17].

### 3.3.12.J| Picking own skin

1) Dermatillomania has been reported with the use of Adderall(R) or Adderall XR(R) [10] [8].

**3.3.12.K] Psychotic disorder****1) Pediatrics**

a) Psychotic or manic symptoms may occur at usual doses among children or adolescents without prior history of psychosis or mania, or may worsen among those with preexisting psychosis. In pooled analyses of multiple short-term clinical studies, new psychotic or manic symptoms occurred in 0.1% of patients treated for several weeks with methylphenidate or amphetamine at usual doses (n=3482) compared with 0% of placebo-treated patients. Consider treatment discontinuation if symptoms occur [10]. [18].

b) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving psychostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil, and dexamethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset [17].

**3.3.12.L] Restlessness**

1) Restlessness has been reported with the use of Adderall(R) or Adderall XR(R) [8] [10].

**3.3.12.M] Volubility**

1) Logorrhea has been reported with the use of Adderall(R) [10].

**3.3.14] Reproductive Effects****3.3.14.A] Priapism**

1) Frequent or prolonged erection have been associated with the use of amphetamine, Adderall(R), or Adderall XR(R) [19].

**3.4] Teratogenicity/Effects in Pregnancy/Breastfeeding****A) Teratogenicity/Effects in Pregnancy**

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

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

**2) Crosses Placenta: Yes**

**3) Clinical Management**

**a)** There are no adequate and well-controlled studies of [amphetamines](#) in pregnant women. A woman who took [dextroamphetamine](#) sulfate with [lovastatin](#) during the first trimester of pregnancy gave birth to a baby with severe congenital bony deformity and other anomalies. Infants born to women who are dependent on [amphetamines](#) have an increased risk of [premature delivery](#), low birth weight, and may experience symptoms of withdrawal ([dysphoria](#), agitation, and significant lassitude). Studies in rodents, using doses similar to those used clinically, indicate that prenatal or early postnatal exposure to [amphetamine](#) (d- or d, l-) can result in long-term neurochemical and behavioral changes. Another study showed hyperactivity and a decrease in weight gain in pregnant rats, as well as decreases in pup survival, pup body weight, gestational weight gain, number of implantations, and number of delivered pups. Therefore, it is recommended that this drug be administered to pregnant women only if the potential benefits to the mother justifies the potential fetal risk [10] [225].

**4) Literature Reports**

**a)** There are no adequate and well-controlled studies of [amphetamines](#) in pregnant women. A woman who took [dextroamphetamine](#) sulfate with [lovastatin](#) during the first trimester of pregnancy gave birth to a baby with severe congenital bony deformity, [tracheo-esophageal fistula](#), and [anal atresia](#) (vater association) [10] [225]. Infants born to women who are dependent on [amphetamines](#) have an increased risk of [premature delivery](#), low birth weight, and may experience symptoms of withdrawal ([dysphoria](#), agitation, and significant lassitude) [10].

**b)** [Amphetamine](#), in the enantiomer ratio present in Adderall XR (d- to l- ratio of 3:1), was given to pregnant rats from gestation day 6 to lactation day 20 in doses of 2, 6, and 10 mg/kg/day (approximately 0.8, 2, and 4 times the maximum recommended human dose (MRHD) for adolescents of 20 mg/day, on a mg/m(2) basis). All doses caused hyperactivity and a decrease in weight gain in the mother rats, as well as a decrease in pup survival. Doses of 6 and 10 mg/kg showed a decrease in pup body weight, correlating with delays in developmental landmarks. Doses of 10 mg/kg caused an increase in pup locomotor activity on day 22 postpartum but not at 5 weeks postweaning. When the pups matured and were tested for reproductive performance, the pups whose mothers had been given 10 mg/kg showed decreases in gestational weight gain, number of implantations, and number of delivered pups [225].

**c)** [Amphetamine](#), in the enantiomer ratio present in Adderall (d- to l- ratio of 3:1), was administered orally throughout organogenesis to pregnant rats in doses of up to 6 mg/kg/day (approximately 1.5 times the MRHD of 30-mg/day child, on a mg/m(2) body surface area basis) and pregnant rabbits in dose of up to 16 mg/kg/day (approximately 8 times the MRHD). It had no apparent effects on embryofetal morphological development. Death, fetal malformations, and maternal toxicity have been observed in mice following [parenteral administration](#) of d-amphetamine in doses of 50 mg/kg/day (approximately 6 times the human dose of 30-mg/day child, on a mg/m(2) basis) or greater [10]. A number of studies in rodents, using doses similar to those used clinically, indicate that prenatal or early postnatal exposure to [amphetamine](#) (d- or d, l-) can result in long-term neurochemical and behavioral changes, including learning and memory deficits, altered locomotor activity, and changes in sexual function [10] [225].

## B)) Breastfeeding

1)) American Academy of Pediatrics Rating: Drugs of abuse for which adverse effects on the infant during breastfeeding have been reported.

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

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

## 3)) Clinical Management

a)) The American Academy of Pediatrics strongly suggests that nursing mothers not ingest drugs of abuse, including [amphetamines](#), which have been associated with irritability and poor sleeping patterns in infants during breastfeeding [226]. Since [amphetamines](#) are excreted in human breast milk, advise women taking [amphetamines](#) to refrain from nursing [10] [225].

## 3.5] Drug Interactions

### 3.5.1] Drug-Drug Combinations

#### 3.5.1.A] [Acetazolamide](#)

1)) Interaction Effect: [amphetamine](#) toxicity ([hypertension](#), [hyperpyrexia](#), seizures)

2)) Summary: Concomitant [acetaZOLAMIDE](#) and [amphetamine](#) therapy resulted in enhanced [amphetamine](#) effects. [AcetaZOLAMIDE](#) produces an alkaline urine and the renal excretion of [amphetamine](#) is decreased due to increased reabsorption [145] [146].

3)) Severity: moderate

4)) Onset: rapid

5)) Substantiation: theoretical

6)) Clinical Management: Lower doses of [dextroamphetamine](#) may be required with urinary alkalinizers. Monitor for [amphetamine](#) toxicity.

7)) Probable Mechanism: decreased renal clearance

#### 3.5.1.B] [Acetazolamide](#)

1)) Interaction Effect: [amphetamine](#) toxicity ([hypertension](#), [hyperpyrexia](#), seizures)

2)) Summary: [AcetaZOLAMIDE](#) tends to alkalinize the urine, increasing the unionized [amphetamine](#) urine concentration, thereby allowing for increased renal tubular reabsorption. Enhanced effects of [amphetamines](#) may occur due to increased [amphetamine](#) concentration [200].

3)) Severity: minor

4)) Onset: delayed

5)) Substantiation: theoretical

6)) Clinical Management: Monitor for [amphetamine](#) toxicity and adjust the dose or discontinue the [acetaZOLAMIDE](#) if necessary.

7)) Probable Mechanism: decreased clearance

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



- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [almotriptan](#) and [dextroamphetamine](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to additive effects and the potential for increased risk of [serotonin syndrome](#) [106]. If coadministration is required, monitoring of patient for signs and symptoms of [serotonin syndrome](#) during treatment and dosage increases may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [almotriptan](#) and [dextroamphetamine](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#) [106]. If coadministration is required, monitoring of patient for signs and symptoms of [serotonin syndrome](#) during treatment and dosage increases may be warranted.
- 7) Probable Mechanism: additive serotonergic effects

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

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [almotriptan](#) and [amphetamine](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment and at dosage increases is recommended if [almotriptan](#) and [amphetamine](#) are used concurrently [106]. 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 [31].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [almotriptan](#) and [amphetamine](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, monitoring of patient during treatment and dosage increases is recommended [106].
- 7) Probable Mechanism: additive serotonergic effect

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

- 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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

#### 3.5.1.F] [Amoxapine](#)

- 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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

### 3.5.1.G] Calamus

1) Interaction Effect: reduced effect of [amphetamines](#)

- 2) Summary: Calamus antagonized spontaneous motor activity and amphetamine-induced hyperactivity in mice [29].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of calamus and [amphetamines](#).
- 7) Probable Mechanism: not specified
- 8) Literature Reports

a) Calamus antagonized spontaneous motor activity and amphetamine-induced hyperactivity in mice. Calamus was administered intraperitoneally (IP) (0.2 milliliters of 10, 25, 50 milligrams/kilogram (mg/kg)). One group of mice received 4 mg/kg [chlorpromazine](#) 30 minutes before calamus injection and spontaneous motor activity was compared to untreated mice. In another test, mice were injected IP with saline, [amphetamine](#) (4.5 mg/kg), or 25 mg/kg calamus followed by [amphetamine](#). Calamus significantly reduced spontaneous motor activity in a manner equivalent to [chlorpromazine](#) at doses of 10 and 25 mg/kg and significantly reduced amphetamine-induced hyperactivity at 25 mg/kg [28].

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

- 1) Interaction Effect: decreased [amphetamine](#) and [chlorproMAZINE](#) effectiveness
- 2) Summary: [Amphetamine](#) may inhibit the antipsychotic effects of [chlorproMAZINE](#) [201] and [chlorproMAZINE](#) may reverse the anorectic effect of [amphetamine](#) [202] [203].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid combining [amphetamines](#) and [chlorproMAZINE](#) where possible.
- 7) Probable Mechanism: antagonism

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

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: Concurrent use of [citalopram](#) and [dextroamphetamine](#) resulted in symptoms of [serotonin syndrome](#) in a 32-year-old male [30]. If [citalopram](#) and [dextroamphetamine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [31].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: A case of [serotonin syndrome](#) was reported with coadministration of [citalopram](#) and [dextroamphetamine](#) [30]. If [citalopram](#) and [dextroamphetamine](#) are used concomitantly, monitor closely for 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 [31].
- 7) Probable Mechanism: additive pharmacologic effects
- 8) Literature Reports

a) A 32-year-old male on [dextroamphetamine](#) experienced [serotonin syndrome](#) approximately 1 week after starting [citalopram](#). He was on [dextroamphetamine](#) 5 mg three times daily for [attention deficit hyperactivity disorder](#). He started 75 mg a day of [venlafaxine](#) for 1 week then the dose was increased to 150 mg daily. Approximately 2 weeks after starting [venlafaxine](#) he experienced marked agitation, anxiety, shivering, and tremor. On admission he was alert and oriented. He experienced diaphoresis, shivering, and fine motor tremor. His heart rate was 140 beats per minute, blood pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No [nystagmus](#) or ocular clonus was noted. Pupils were 3 mm diameter and reactive. He had generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerking, and unilateral-tonic spasm of his orbicularis oris muscle. No abnormality was shown on ECG, except [sinus tachycardia](#) with a baseline tremor. [Dextroamphetamine](#) and [venlafaxine](#) were discontinued and [cyproheptadine](#) (up to a total of 32 mg over 3 hours) was administered. Symptoms resolved and he was discharged the following morning. [Dextroamphetamine](#) was restarted 3 days later. Four days later [citalopram](#) was started. Approximately 1 week later, he experienced similar symptoms as he did with [dextroamphetamine](#) and [venlafaxine](#). Agitation, nausea, diarrhea, and teeth clenching were still present 3 days after [citalopram](#) was discontinued. Two doses of [cyproheptadine](#) were given and within 2 days he was asymptomatic [30].

### 3.5.1.J] Clobazam

- 1) Interaction Effect: increased [amphetamine](#) plasma concentrations
- 2) Summary: The concomitant use of [amphetamine](#), a CYP2D6 substrate [1], and clobazam, a CYP2D6 inhibitor, may cause increased [amphetamine](#) plasma concentrations. Although no formal drug interaction studies have been done with [amphetamine](#), in a drug interaction study of the concomitant use of a single dose of [dextromethorphan](#) (also a CYP2D6 substrate) and clobazam, there were increases in AUC and Cmax. Dose reduction of [amphetamine](#) may be required when coadministered with clobazam [215].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [amphetamine](#) with clobazam may cause increased [amphetamine](#) plasma concentrations. If concomitant use is required, dose reduction may be warranted for [amphetamine](#) [215].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [amphetamine](#) metabolism by clobazam
- 8) Literature Reports

a) Although no formal studies have been done with [amphetamine](#), in a drug interaction study of the concomitant use of a single dose of [dextromethorphan](#) (also a CYP2D6 substrate) and clobazam, there was a 90% increase in AUC and a 59% increase in Cmax [215].

### 3.5.1.K] Clomipramine

- 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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

### 3.5.1.L] Clorgyline

1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2) Summary: Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [129]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of monoamine oxidase inhibitors (MAOIs) results in more [norepinephrine](#)

being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use leads to greater amounts of [norepinephrine](#), which increases sympathetic activity [130]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [131] [132] [133] [134]. Some efficacy with the combination of [dextroamphetamine](#) or [pemoline](#) in addition to a MAOI was observed during a study of patients with treatment-refractory depression [135].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.

7) Probable Mechanism: increased [norepinephrine](#) availability

8) Literature Reports

a) Severe headaches and hypertensive crises are well-documented in the literature as being associated with this combination. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [127].

b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system (CNS) stimulant ([pemoline](#) or [dextroamphetamine](#)) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. Most of the patients (78%) experienced remission of symptoms for at least six months during coadministration, and 31% of the patients continued treatment after the study. Four of the patients taking [pemoline](#) and a MAOI discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or shakiness. Three of the patients taking [dextroamphetamine](#) and a MAOI discontinued the medications due to memory problems, parkinsonian symptoms, [somnambulism](#), or weight gain. Six patients experienced mood cycling, five to [hypomania](#) and one to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [128].

### 3.5.1.M] Clorgyline

1) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2) Summary: The concurrent use of [amphetamine](#) and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse following the discontinuation of MAOIs before [amphetamine](#) therapy is instituted [209]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [210].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: [Amphetamine](#) use is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors.

7) Probable Mechanism: increased [norepinephrine](#) availability

8) Literature Reports

a) Severe headaches and hypertensive crises are well-documented in the literature as being associated with this combination. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [208].



**3.5.1.N] Desipramine**

- 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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

### 3.5.1.O] Desvenlafaxine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) (hypertension, tachycardia, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Desvenlafaxine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy [123].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution with coadministration of desvenlafaxine and another serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Immediate discontinuation of both agents and supportive symptomatic treatment is warranted if [serotonin syndrome](#) develops [123].
- 7) Probable Mechanism: additive serotonergic effect

### 3.5.1.P] Dolasetron

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of [dolasetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#). Discontinue treatment with [dolasetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur [159] [160].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [dolasetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#). Discontinue treatment with [dolasetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur [159] [160].
- 7) Probable Mechanism: unknown

### 3.5.1.Q] Donepezil

- 1) Interaction Effect: lower seizure threshold
- 2) Summary: Seizure threshold lowering effects have been associated with [donepezil](#) [124]. Use extreme caution when prescribing [donepezil](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.
- 3) Severity: major



- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Seizure threshold lowering effects have been associated with [donepezil](#) [124]. Use extreme caution when prescribing [donepezil](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.
- 7) Probable Mechanism: unknown

### 3.5.1.R] Dothiepin

- 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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

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

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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

### 3.5.1.T] [Fentanyl](#)

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

2) Summary: [Fentanyl](#) is proserotonergic and has been associated with [serotonin syndrome](#) when coadministered with serotonergic drugs [75], including SSRIs [77] [76] [78]. [Serotonin syndrome](#) may also result from concomitant use of [fentanyl](#) with serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, or other synthetic piperidine opioids. If possible, consider replacing serotonergic opioids with non-serotonergic opioids [75]. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic hyperactivity, and mental status changes. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [31].

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: [Fentanyl](#) is a proserotonergic, synthetic piperidine opioid and has been associated with [serotonin syndrome](#) when coadministered with other serotonergic drugs. Therefore, use caution with coadministration of [fentanyl](#) and a serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, tricyclic antidepressant, or another synthetic piperidine opioid, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If possible, consider replacing serotonergic opioids (eg, [fentanyl](#)) with non-serotonergic opioids (eg, [morphine](#)) [75]. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, diarrhea), and mental status changes (eg, agitation, [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [31].

7) Probable Mechanism: additive serotonergic effect

8) Literature Reports

a) [Serotonin syndrome](#) associated with [fentanyl](#) use during an [esophagogastroduodenoscopy](#) was reported in a 39-year-old woman also taking [sertraline](#) 100 mg daily as an outpatient. The patient initially presented with [hematemesis](#) and a history of [alcoholic cirrhosis](#). Prior to the [esophagogastroduodenoscopy](#), an [octreotide](#) and [pantoprazole](#) drip was started, 2 doses of

50 micrograms, and 2 doses of midazolam 1 mg were administered. The patient became somnolent and extremely rigid in all four extremities following the procedure, and vecuronium and etomidate were given for immediate intubation. The rigidity progressed with diffuse diaphoresis, horizontal roving eye movements, and a fever of 105 degrees F. Due to the potential for seizure activity, lorazepam 2 mg IV was given with no improvement and a propofol drip was started for continued sedation during intubation. A CPK value of 2800 units/L and an ammonia level of 340 micromols/L indicated rhabdomyolysis. An acute intracranial process was ruled out on a CT scan of the brain and the neurology team made the diagnosis of serotonin syndrome secondary to an interaction between fentanyl and sertraline. Propofol was continued for sedation and the patient received supportive treatment with a cooling blanket and cyproheptadine. After 3 days, the patient's temperature and CPK level normalized and she later extubated with no further complications [76].

b) Serotonin syndrome following the administration of IV fentanyl during surgical procedures was reported in 2 patients also taking SSRIs (sertraline and escitalopram). The first patient received IV fentanyl (50 micrograms), midazolam (2 mg), and 2 doses propofol (60 mg and 40 mg) in an outpatient surgery center prior to a carpal tunnel release procedure. Postoperatively the patient began shivering and became increasingly agitated for which she was transferred to the emergency department. On presentation the patient was combative, diaphoretic, confused, was unable to follow commands, tachycardic, hypertensive, had hyperreflexia, and ankle clonus. Baseline creatinine kinase rose to 613 units/L on day 2 of hospitalization. The toxicology service treated her with escalating doses of benzodiazepines with no improvement. The patient was subsequently intubated and sedated with a continuous propofol infusion. After 2 days the patient was extubated and by day 3 all symptoms had resolved and the patient was discharged home. The second patient was a 59-year-old woman admitted for an omentectomy for which she received IV fentanyl 250 micrograms, etomidate, vecuronium, morphine and cephazolin. Following extubation the patient became hypoxic and acidotic and was reintubated and transferred to the ICU. On postoperative day 1 she was extubated and later became tachycardic and was unable to follow commands. On examination the patient was agitated and diaphoretic, had patellar hyperreflexia and a bilateral 3 to 4 beat ankle clonus. Laboratory evaluation was remarkable for a peak creatine kinase of 1161 units/L on postoperative day 2. The patient was treated with lorazepam and cyproheptadine with resolution of symptoms after 3 days [77].

c) A case of postoperative serotonin syndrome following the administration of fentanyl for general anesthesia and post operative analgesia was reported in a 60-year-old woman also receiving paroxetine. Outpatient medications included only paroxetine and thyroxine for a history of depression and hypothyroidism. The patient was admitted for an extensive resection of a recurrent left chest wall myxofibrosarcoma and given propofol and 200 micrograms (mcg) of fentanyl for the induction of anesthesia. The patient also received an additional 800 mcg of fentanyl (intermittent 50 mcg boluses) intraoperatively and a subsequent fentanyl infusion (100 to 200 mcg/hr) for postoperative sedation and analgesia (2545 mcg of fentanyl received over 36 hours). The fentanyl infusion was continued 36 hours postoperatively, at which time intermittent agitation, bilateral hypertonia and hyperreflexia, and bilateral inducible ankle clonus were observed on neurological examination. Symptoms were more severe in the lower limbs and on the right side of the body. A CT scan of the brain was unremarkable and all other examination findings, including a thyroid function test, were within normal limits with the exception of elevated blood pressure (180/90 mmHg), which spontaneously resolved 24 hours after the procedure. Fentanyl was discontinued, and 24 hours later, there was marked improvement in neurological symptoms and complete recovery by postoperative day 4. The patient was ultimately discharged home with no further complications [78].

### 3.5.1.U] Fluoxetine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: [Serotonin syndrome](#) may the result from concomitant use of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic instability, and mental status changes, especially during treatment initiation and dose increases. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care [161].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Exercise caution with coadministration of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants, because it may result in a life-threatening condition called [serotonin syndrome](#). If these agents are used together, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care [161]
- 7) Probable Mechanism: additive serotonergic effect

### 3.5.1.V] Furazolidone

- 1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: [Furazolidone](#) has significant MAOI activity [20] [21]. Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [22]. Sympathomimetics with indirect/mixed activity such as [dextroamphetamine](#) cause the release of [norepinephrine](#), and the use of MAOIs results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [23]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in serious [hypertension](#) [24] [25] [26] [27].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.
- 7) Probable Mechanism: increased [norepinephrine](#) availability

### 3.5.1.W] Furazolidone

- 1) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: [Furazolidone](#) has significant MAOI activity [166] [167] and should not be used concurrently with sympathomimetics. Sympathomimetics with indirect/mixed activity such as [amphetamine](#) cause the release of [norepinephrine](#), and the use of MAO Inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [168]. Coadministration of indirect-acting sympathomimetics and MAO Inhibitors has resulted in serious [hypertension](#) [169] [170] [171] [172].
- 3) Severity: major
- 4) Onset: rapid

- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [amphetamines](#) and an MAO inhibitor, or medications with MAO Inhibitor activity, should be avoided.
- 7) Probable Mechanism: increased [norepinephrine](#) availability

#### 3.5.1.X] [Granisetron](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of [granisetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Instruct patients of the increased risk of [serotonin syndrome](#) with concurrent use of these drugs. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur [156].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [granisetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Instruct patients of the increased risk of [serotonin syndrome](#) with concurrent use of these drugs. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur [156].
- 7) Probable Mechanism: unknown

#### 3.5.1.Y] [Guanethidine](#)

- 1) Interaction Effect: decreased [guanethidine](#) effectiveness
- 2) Summary: [Amphetamines](#) displace [guanethidine](#) from the neuron and interfere with neuron uptake. If possible avoid concurrent use of these medications [207].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patient for signs of decreased [guanethidine](#) effectiveness. Adjust the dosage of [guanethidine](#) if necessary.
- 7) Probable Mechanism: antagonism
- 8) Literature Reports

a) Concomitant [guanethidine](#) and [amphetamine](#) administration has been reported to result in antagonism of the hypotensive effects of [guanethidine](#). It appears that [amphetamine](#) displaces [guanethidine](#) from its site of action thereby reversing its hypotensive effects [204] [205].

b) Available data indicate that [amphetamine](#) does not alter the orthostatic hypotension seen with [guanethidine](#) but will result in an increase in supine systolic blood pressure [206] [205].

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

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2) Summary: Both [dextroamphetamine](#) and [hydroxytryptophan](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [dextroamphetamine](#) and [hydroxytryptophan](#) are used concurrently.
- 3) Severity: major
- 4) Onset: unspecified



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

### 3.5.1.AA] Hydroxytryptophan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amphetamines](#) and hydroxytryptophan affect the serotonergic neurotransmitter systems. The concomitant use of hydroxytryptophan with [amphetamines](#) may cause [serotonin syndrome](#) due to additive serotonergic effects and coadministration should be approached with caution. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [amphetamines](#) and hydroxytryptophan are used concurrently.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of an [amphetamine](#) with hydroxytryptophan may result in additive serotonergic effects and risk of [serotonin syndrome](#) and should be approached with caution. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effects

### 3.5.1.AB] Imipramine

- 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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].

- b)) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].
- c)) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].
- d)) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].
- e)) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].
- f)) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

### 3.5.1.AC] Ioflupane I 123

- 1)) Interaction Effect: interference with ioflupane I 123 imaging
- 2)) Summary: The ioflupane component of ioflupane I 123 binds to the [dopamine](#) transporter allowing for striatal [dopamine](#) transport visualization using [single photon emission computed tomography](#) (SPECT) [brain imaging](#). Because [amphetamine](#) binds with high affinity to the [dopamine](#) transporter, there is the potential for interference with ioflupane I 123 imaging. It is unknown whether discontinuing [amphetamine](#) prior to ioflupane I 123 administration may minimize this interference [196]. The potential for imaging interference should be considered when administering ioflupane I 123 to patients who are already receiving [amphetamine](#).
- 3)) Severity: moderate
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [amphetamine](#) and ioflupane I 123 may result in interference with ioflupane I 123 imaging. It is unknown whether discontinuing [amphetamine](#) prior to ioflupane I 123 administration may minimize the interference [196]. Consider the potential for imaging interference when administering ioflupane I 123 to patients who are already receiving [amphetamine](#).
- 7)) Probable Mechanism: unknown

### 3.5.1.AD] Iproniazid

- 1)) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))



2) Summary: Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [99]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of monoamine oxidase inhibitors (MAOIs) results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use leads to greater amounts of [norepinephrine](#), which increases sympathetic activity [100]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [101] [102] [103] [104]. Some efficacy with the combination of [dextroamphetamine](#) or [pemoline](#) in addition to a MAOI was observed during a study of patients with treatment-refractory depression [105].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.

7) Probable Mechanism: increased [norepinephrine](#) availability

8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system (CNS) stimulant ([pemoline](#) or [dextroamphetamine](#)) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. Most of the patients (78%) experienced remission of symptoms for at least six months during coadministration, and 31% of the patients continued treatment after the study. Four of the patients taking [pemoline](#) and a MAOI discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or shakiness. Three of the patients taking [dextroamphetamine](#) and a MAOI discontinued the medications due to memory problems, parkinsonian symptoms, [somnambulism](#), or weight gain. Six patients experienced mood cycling, five to [hypomania](#) and one to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [98].

### 3.5.1.AE] Iproniazid

1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2) Summary: The concurrent use of [amphetamine](#) and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse following the discontinuation of MAOIs before [amphetamine](#) therapy is instituted [216]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [217]. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [218].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Amphetamine](#) use is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors.

7) Probable Mechanism: increased [norepinephrine](#) availability

### 3.5.1.AF] Isocarboxazid

1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2) Summary: Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [81] [82]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAOIs results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use leads to greater amounts of [norepinephrine](#), which increases sympathetic activity [83]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [84] [85] [86] [87]. Some efficacy with the combination of [dextroamphetamine](#) or [pemoline](#) in addition to a MAOI was observed during a study of patients with treatment-refractory depression [88].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.

7) Probable Mechanism: increased [norepinephrine](#) availability

8) Literature Reports

a) Severe headaches and hypertensive crises are well-documented in the literature with this combination. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [79].

b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system (CNS) stimulant ([pemoline](#) or [dextroamphetamine](#)) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. Most of the patients (78%) experienced remission of symptoms for at least six months during coadministration, and 31% of the patients continued treatment after the study. Four of the patients taking [pemoline](#) and a MAOI discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or shakiness. Three of the patients taking [dextroamphetamine](#) and a MAOI discontinued the medications due to memory problems, parkinsonian symptoms, [somnambulism](#), or weight gain. Six patients experienced mood cycling, five to [hypomania](#) and one to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [80].

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

1) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2) Summary: The concurrent use of [amphetamine](#) and monoamine oxidase inhibitors (MAOIs) is contraindicated [192]. At least 14 days should elapse following the discontinuation of MAOIs before [amphetamine](#) therapy is instituted [193]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [194] [195].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: [Amphetamine](#) use is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors.

7) Probable Mechanism: increased [norepinephrine](#) availability

8) Literature Reports

a)) Severe headaches and hypertensive crises are well-documented in the literature with this combination. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [190].

b)) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system (CNS) stimulant ([pemoline](#) or [dextroamphetamine](#)) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. Most of the patients (78%) experienced remission of symptoms for at least six months during coadministration, and 31% of the patients continued treatment after the study. Four of the patients taking [pemoline](#) and a MAOI discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or shakiness. Three of the patients taking [dextroamphetamine](#) and a MAOI discontinued the medications due to memory problems, parkinsonian symptoms, [somnambulism](#), or weight gain. Six patients experienced mood cycling, five to [hypomania](#) and one to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [191].

### 3.5.1.AH] Levomilnacipran

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

2)) Summary: Levomilnacipran is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of potentially life-threatening [serotonin syndrome](#) and should be approached with extreme caution. If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy [162].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use extreme caution with coadministration of levomilnacipran and another serotonergic drug, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops [162].

7)) Probable Mechanism: additive serotonergic effects

### 3.5.1.AI] Lofepramine

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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

### 3.5.1.AJ] Lorcaserin

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic neurotransmitter system, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life threatening and symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#),

labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy [157].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with concomitant administration of lorcaserin and another serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops [157].

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.AK] [Meperidine](#)

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

2) Summary: [Meperidine](#) is considered a proserotonergic opioid and has been associated with [serotonin syndrome](#) when used concomitantly with other serotonergic agents [75]. Increased serotonin levels which may produce additive serotonergic effects can occur if serotonergic agents are taken concurrently with [meperidine](#). Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [31]. Use caution if [meperidine](#) and a serotonergic agent are coadministered and monitor patients for signs and symptoms of [serotonin syndrome](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.AL] [Mirtazapine](#)

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

2) Summary: Concomitant use of [mirtazapine](#) with other serotonergic agents may increase the risk of [serotonin syndrome](#) due to additive serotonergic effects. Monitor for symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases, and if the patient shows symptoms, treatment with [mirtazapine](#) and any concomitant serotonergic agent should be discontinued [33]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops after discontinuation of the offending agents, provide supportive care and other therapy as necessary [31].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: If concomitant use with other serotonergic drugs is clinically warranted, monitor for the emergence of [serotonin syndrome](#), particularly during treatment initiation and dose increases. Discontinue use of both agents, if a patient shows symptoms of [serotonin syndrome](#) [33].
- 7) Probable Mechanism: additive serotonin effects
- 8) Literature Reports

a) Within a few hours of starting [mirtazapine](#) and shortly after stopping [fluoxetine](#), a 75-year-old woman experienced symptoms consistent with [serotonin syndrome](#). Current medication for depression included [fluoxetine](#), [chlorpromazine](#), and [lorazepam](#). Due to lack of response, [fluoxetine](#) was discontinued and soon afterward [mirtazapine](#) 30 mg/day was started. Within a few hours of starting [mirtazapine](#), she experience dizziness, headache, nausea, dry mouth, intense anxiety and agitation with suicidal ideas. Other symptoms were difficulty walking, marked resting tremor of the hands, and insomnia. Over the next 3 days, she progressively worsened. [Mirtazapine](#) was discontinued on day 5. Her symptoms improved the following day. [Fluoxetine](#) 20 mg/day was restarted on day 7 with subsequent resolution of dizziness, nausea, headache, and agitation resolution over the following days. Over the next 10 days, tremor, anxiety, difficulty walking, dry mouth, and insomnia improved [34].

b) A 26-year-old woman with [anorexia nervosa](#) receiving [fluvoxamine](#) for 4 months developed symptoms of [serotonin syndrome](#) after [mirtazapine](#) was initiated. The symptoms of twitching, tremors, agitation, restlessness, and "feeling like she could crawl out of her skin" developed over a period of 4 days after starting [mirtazapine](#) 30 mg/day. Symptoms rapidly progressed to twitching, tremors, and restlessness. She was hospitalized with further symptoms of diaphoresis, flushing, fasciculations, and nausea and treated with [cyproheptadine](#), [acetaminophen](#), and IV fluids. She remained afebrile throughout the event. Symptoms completely resolved within 24 hours [35].

### 3.5.1.AM] Moclobemide

- 1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [116]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of monoamine oxidase inhibitors (MAOIs) results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use leads to greater amounts of [norepinephrine](#), which increases sympathetic activity [117]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [118] [119] [120] [121]. Some efficacy with the combination of [dextroamphetamine](#) or [pemoline](#) in addition to a MAOI was observed during a study of patients with treatment-refractory depression [122].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.
- 7) Probable Mechanism: increased [norepinephrine](#) availability
- 8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system (CNS) stimulant ([pemoline](#) or [dextroamphetamine](#))



with a monoamine oxidase inhibitor (MAOI) was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. Most of the patients (78%) experienced remission of symptoms for at least six months during coadministration, and 31% of the patients continued treatment after the study. Four of the patients taking [pemoline](#) and a MAOI discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or shakiness. Three of the patients taking [dextroamphetamine](#) and a MAOI discontinued the medications due to memory problems, parkinsonian symptoms, [somnambulism](#), or weight gain. Six patients experienced mood cycling, five to [hypomania](#) and one to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [115].

### 3.5.1.AN] Moclobemide

- 1) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: The concurrent use of [amphetamine](#) and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse following the discontinuation of MAOIs before [amphetamine](#) therapy is instituted [182]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [183]. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [184].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: [Amphetamine](#) use is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors.
- 7) Probable Mechanism: increased [norepinephrine](#) availability

### 3.5.1.AO] Nialamide

- 1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [68]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of monoamine oxidase inhibitors (MAOIs) results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use leads to greater amounts of [norepinephrine](#), which increases sympathetic activity [69]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [70] [71] [72] [73]. Some efficacy with the combination of [dextroamphetamine](#) or [pemoline](#) in addition to a MAOI was observed during a study of patients with treatment-refractory depression [74].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.
- 7) Probable Mechanism: increased [norepinephrine](#) availability
- 8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system (CNS) stimulant ([pemoline](#) or [dextroamphetamine](#)) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the patients were also



taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. Most of the patients (78%) experienced remission of symptoms for at least six months during coadministration, and 31% of the patients continued treatment after the study. Four of the patients taking [pemoline](#) and a MAOI discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or shakiness. Three of the patients taking [dextroamphetamine](#) and a MAOI discontinued the medications due to memory problems, parkinsonian symptoms, [somnambulism](#), or weight gain. Six patients experienced mood cycling, five to [hypomania](#) and one to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [67].

### 3.5.1.AP] Nialamide

- 1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: The concurrent use of [amphetamine](#) and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse following the discontinuation of MAOIs before [amphetamine](#) therapy is instituted [176]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAOIs results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [177]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [178] [179] [180] [181].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: [Amphetamine](#) use is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors.
- 7) Probable Mechanism: increased [norepinephrine](#) availability

### 3.5.1.AQ] Nortriptyline

- 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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].

**b))** Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].

**c))** A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].

**d))** Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].

**e))** Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].

**f))** There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

### 3.5.1.AR] Opipramol

**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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].
- b) Human pharmacologic studies have demonstrated that **methylphenidate** may inhibit the metabolism of some tricyclic antidepressants, such as **imipramine**, **clomipramine**, or **desipramine** [56].
- c) A 55-year-old female patient was maintained on **imipramine** 350 mg daily for several years, with **imipramine** plus **desipramine** blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with **fenfluramine** 20 mg three times daily, the patient fell asleep while driving. The **imipramine** plus **desipramine** level was 704 mcg/L. **Fenfluramine** may have inhibited the CYP450 isoenzyme responsible for metabolizing **imipramine** [57].
- d) Concomitant administration of tricyclic antidepressants and **methylphenidate** can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the **methylphenidate** usually results in the blood pressure returning to normotensive levels; reinstitution of the **methylphenidate** resulted in further blood pressure elevation [58] [55].
- e) Fifteen patients with DSM-III **major depression**, who failed to respond to treatment with **desipramine** given for at least four weeks, were given **fenfluramine** 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, **fenfluramine** more than doubled steady-state plasma levels of **desipramine** [59].
- f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

3.5.1.AS] **Palonosetron**

- 1) Interaction Effect: increased risk of **serotonin syndrome**
- 2) Summary: Concomitant use of **mirtazapine** with other serotonergic agents may increase the risk of **serotonin syndrome**. Monitor for the emergence of **serotonin syndrome**; symptoms include mental status changes (eg, agitation, hallucinations, **delirium**, coma), autonomic instability (eg, **tachycardia**, labile blood pressure, dizziness, diaphoresis, flushing, **hyperthermia**), neuromuscular abnormalities (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without, gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Discontinue use of **palonosetron** and begin supportive treatment if the patient exhibits signs and symptoms of **serotonin syndrome** [32].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: If concomitant use with other serotonergic drugs is clinically warranted, monitor for the emergence of **serotonin syndrome**. Discontinue use of **palonosetron** and begin supportive treatment if the patient exhibits signs and symptoms of **serotonin syndrome** [32].

7J) Probable Mechanism: unknown

### 3.5.1.AT] Pargyline

1J) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2J) Summary: Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [47]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAOIs results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [48]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [49] [50] [51] [52].

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.

7J) Probable Mechanism: increased [norepinephrine](#) availability

### 3.5.1.AU] Pargyline

1J) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2J) Summary: The concurrent use of [amphetamine](#) and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse following the discontinuation of MAOIs before [amphetamine](#) therapy is instituted [219]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [220]. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [221].

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: [Amphetamine](#) use is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors.

7J) Probable Mechanism: increased [norepinephrine](#) availability

### 3.5.1.AV] Phenelzine

1J) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2J) Summary: [Amphetamines](#) cause the release of [norepinephrine](#), and the use of monoamine oxidase inhibitors (MAOIs) results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use leads to greater amounts of [norepinephrine](#), which increases sympathetic activity [149]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [150] [151] [152] [153]. Some efficacy with the combination of [dextroamphetamine](#) or [pemoline](#) in addition to a MAOI was observed during a study of patients with treatment-refractory depression [154]. However, the concurrent use of [dextroamphetamine](#) and [phenelzine](#) is contraindicated [155].

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.

7J) Probable Mechanism: increased [norepinephrine](#) availability

8J) Literature Reports

aJ) Severe headaches and hypertensive crises are well-documented in the literature with this combination. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [147].

bJ) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system (CNS) stimulant ([pemoline](#) or [dextroamphetamine](#)) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. Most of the patients (78%) experienced remission of symptoms for at least six months during coadministration, and 31% of the patients continued treatment after the study. Four of the patients taking [pemoline](#) and a MAOI discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or shakiness. Three of the patients taking [dextroamphetamine](#) and a MAOI discontinued the medications due to memory problems, parkinsonian symptoms, [somnambulism](#), or weight gain. Six patients experienced mood cycling, five to [hypomania](#) and one to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [148].

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

1J) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2J) Summary: The concurrent use of [amphetamine](#) and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse following the discontinuation of MAOIs before [amphetamine](#) therapy is instituted [197]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [198]. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [199].

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: established

6J) Clinical Management: [Amphetamine](#) use is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors.

7J) Probable Mechanism: increased [norepinephrine](#) availability

### 3.5.1.AX] [Procarbazine](#)

1J) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2J) Summary: Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [108]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of monoamine oxidase inhibitors (MAOIs) results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use leads to greater amounts of [norepinephrine](#), which increases sympathetic activity [109]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [110] [111] [112] [113]. Some efficacy with the combination of [dextroamphetamine](#) or [pemoline](#) in addition to a MAOI was observed during a study of patients with treatment-refractory depression [114].

3J) Severity: contraindicated

4J) Onset: rapid

- 5) Substantiation: probable
- 6) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.
- 7) Probable Mechanism: increased [norepinephrine](#) availability
- 8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system (CNS) stimulant ([pemoline](#) or [dextroamphetamine](#)) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. Most of the patients (78%) experienced remission of symptoms for at least six months during coadministration, and 31% of the patients continued treatment after the study. Four of the patients taking [pemoline](#) and a MAOI discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or shakiness. Three of the patients taking [dextroamphetamine](#) and a MAOI discontinued the medications due to memory problems, parkinsonian symptoms, [somnambulism](#), or weight gain. Six patients experienced mood cycling, five to [hypomania](#) and one to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [107].

### 3.5.1.AY] [Procarbazine](#)

- 1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: The concurrent use of [amphetamine](#) and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse following the discontinuation of MAOIs before [amphetamine](#) therapy is instituted [163]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [164]. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [165].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: [Amphetamine](#) use is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors.
- 7) Probable Mechanism: increased [norepinephrine](#) availability

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

- 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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical



6j) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [53] [54] [2] [55]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7j) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8j) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [53] [54] [2].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

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

1j) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#)) and [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2j) Summary: [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [185]. Severe hypertensive reactions have been reported following the administration of non-selective MAO inhibitors and sympathomimetics. A minimum of 14 days should elapse after discontinuing [rasagiline](#) before initiating therapy with [amphetamine](#) [186].

3j) Severity: contraindicated



- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of [amphetamine](#) and [rasagiline](#) is contraindicated. Allow 14 days to elapse between the discontinuation of [rasagiline](#) and the initiation of therapy with [amphetamine](#).
- 7) Probable Mechanism: increased [norepinephrine](#) availability

### 3.5.1.BB] [Selegiline](#)

- 1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [41]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAOIs results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [42]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [43] [44] [45] [46].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.
- 7) Probable Mechanism: increased [norepinephrine](#) availability
- 8) Literature Reports

- a) Severe headaches and hypertensive crises are well-documented in the literature as being associated with this combination. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [40].

### 3.5.1.BC] [Selegiline](#)

- 1) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#)) and [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: The concurrent use of [amphetamine](#) and [selegiline](#) is contraindicated. At least 14 days should elapse following the discontinuation of [selegiline](#) before [amphetamine](#) therapy is instituted and a minimum of 7 days should elapse after discontinuing [propoxyphene](#) before initiating therapy with [selegiline](#) [212] [213]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [185].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: established
- 6) Clinical Management: The concurrent use of [amphetamine](#) and [selegiline](#) is contraindicated. Allow 14 days to elapse between the discontinuation of [selegiline](#) and the initiation of therapy with [amphetamine](#) or allow a minimum of 7 days to elapse between the discontinuation of the [amphetamine](#) and the initiation of therapy with [selegiline](#).
- 7) Probable Mechanism: increased [norepinephrine](#) availability
- 8) Literature Reports

- a) Severe headaches and hypertensive crises are well-documented in the literature as being associated with this combination. Other potential reactions include [cardiac arrhythmias](#), chest pain, circulatory failure, [hyperpyrexia](#), and death [211].

**3.5.1.BD] Sibutramine**

- 1) Interaction Effect: an increased risk of [hypertension](#) and [tachycardia](#)
- 2) Summary: [Sibutramine](#) has been associated with substantial increases in blood pressure and heart rate in some patients. Although the concurrent administration of [sibutramine](#) and other centrally acting appetite suppressants has not been systematically evaluated, it is possible that severe [hypertension](#) and [tachycardia](#) may result. Therefore, the concurrent administration of [sibutramine](#) with another centrally acting appetite suppressant is contraindicated [125].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant administration of [sibutramine](#) with other centrally active appetite suppressant agents is contraindicated.
- 7) Probable Mechanism: additive pharmacologic effects

**3.5.1.BE] Sodium Bicarbonate**

- 1) Interaction Effect: [amphetamine](#) toxicity ([hypertension](#), [hyperpyrexia](#), seizures)
- 2) Summary: [Sodium bicarbonate](#) (ie, greater than 2 grams daily) may alkalinize the urine, increasing the unionized [amphetamine](#) urine concentration and allowing for increased renal tubular reabsorption. Enhanced effects of [amphetamine](#) may occur due to increased [amphetamine](#) concentrations [158].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Lower doses of [dextroamphetamine](#) may be required with urinary alkalinizers. Monitor for [amphetamine](#) toxicity.
- 7) Probable Mechanism: decreased [dextroamphetamine](#) clearance

**3.5.1.BF] Sodium Bicarbonate**

- 1) Interaction Effect: [amphetamine](#) toxicity ([hypertension](#), [hyperpyrexia](#), seizures)
- 2) Summary: [Sodium bicarbonate](#) (ie, greater than 2 grams daily) may alkalinize the urine, increasing the unionized [amphetamine](#) urine concentration and allowing for increased renal tubular reabsorption. Enhanced effects of [amphetamine](#) may occur due to increased serum [amphetamine](#) concentrations [214].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for possible [amphetamine](#) toxicity (eg, [hypertension](#), [hyperpyrexia](#), or seizures) and decrease the dose as needed.
- 7) Probable Mechanism: decreased renal clearance

**3.5.1.BG] Toloxatone**

- 1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [91]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of monoamine oxidase inhibitors (MAOIs) results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use leads to greater amounts of [norepinephrine](#), which increases sympathetic activity [92]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#)

and [hyperpyrexia](#) [93] [94] [95] [96]. Some efficacy with the combination of [dextroamphetamine](#) or [pemoline](#) in addition to a MAOI was observed during a study of patients with treatment-refractory depression [97].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.

7) Probable Mechanism: increased [norepinephrine](#) availability

8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system (CNS) stimulant ([pemoline](#) or [dextroamphetamine](#)) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. Most of the patients (78%) experienced remission of symptoms for at least six months during coadministration, and 31% of the patients continued treatment after the study. Four of the patients taking [pemoline](#) and a MAOI discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or shakiness. Three of the patients taking [dextroamphetamine](#) and a MAOI discontinued the medications due to memory problems, parkinsonian symptoms, [somnia](#), or weight gain. Six patients experienced mood cycling, five to [hypomania](#) and one to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [90].

### 3.5.1.BH] Toloxatone

1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2) Summary: The concurrent use of [amphetamine](#) and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse following the discontinuation of MAOIs before [amphetamine](#) therapy is instituted [173]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [174]. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [175]. As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of [amphetamine](#) to the same frequency, extent, and duration observed with other MAOIs. However, until further studies confirm the safety and efficacy of this combined therapy, concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Amphetamine](#) use is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors.

7) Probable Mechanism: increased [norepinephrine](#) availability

### 3.5.1.BI] Tramadol

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

2) Summary: Use caution when coadministering [tramadol](#), including use within the recommended dose range, and a serotonergic agent as this may increase the risk for [serotonin syndrome](#). If concomitant use of [tramadol](#) with a serotonergic agent is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation and dosage increases [39].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [tramadol](#), including use within the recommended dose range, with serotonergic agents may increase the risk for [serotonin syndrome](#) and should be undertaken with caution. If concomitant use of [tramadol](#) with a serotonergic agent is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation and dosage increases [39].
- 7) Probable Mechanism: additive serotonergic effects

### 3.5.1.BJ] [Tranlycypromine](#)

- 1) Interaction Effect: a [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: Use of [dextroamphetamine](#) concomitantly or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated [138]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of monoamine oxidase inhibitors (MAOIs) results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use leads to greater amounts of [norepinephrine](#), which increases sympathetic activity [139]. Coadministration of indirect-acting sympathomimetics and MAOIs has resulted in severe [hypertension](#) and [hyperpyrexia](#) [140] [141] [142] [143]. Some efficacy with the combination of [dextroamphetamine](#) or [pemoline](#) in addition to a MAOI was observed during a study of patients with treatment-refractory depression [144].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: [Dextroamphetamine](#) use during or within 14 days following the administration of a monoamine oxidase inhibitor is contraindicated.
- 7) Probable Mechanism: increased [norepinephrine](#) availability
- 8) Literature Reports

a) Severe headaches and hypertensive crises are well-documented in the literature with this combination. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [136].

b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system (CNS) stimulant ([pemoline](#) or [dextroamphetamine](#)) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. Most of the patients (78%) experienced remission of symptoms for at least six months during coadministration, and 31% of the patients continued treatment after the study. Four of the patients taking [pemoline](#) and a MAOI discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or shakiness. Three of the patients taking [dextroamphetamine](#) and a MAOI discontinued the medications due to memory problems, parkinsonian symptoms, [somnambulism](#), or weight gain. Six patients experienced mood cycling, five to [hypomania](#) and one to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [137].

### 3.5.1.BK] [Tranlycypromine](#)

- 1) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))

2) Summary: The concurrent use of [amphetamine](#) and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse following the discontinuation of MAOIs before [amphetamine](#) therapy is instituted [187]. [Amphetamines](#) cause the release of [norepinephrine](#), and the use of MAO inhibitors results in more [norepinephrine](#) being made available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amounts of [norepinephrine](#) which increases sympathetic activity [188]. Other potential reactions include [cardiac arrhythmias](#), chest pain, [hyperpyrexia](#), and death [189].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: [Amphetamine](#) use is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors.

7) Probable Mechanism: increased [norepinephrine](#) availability

### 3.5.1.BL] [Trazodone](#)

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

2) Summary: Both [dextroamphetamine](#) 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](#) [38]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [dextroamphetamine](#) and [trazodone](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [31].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [dextroamphetamine](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#) [38]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.BM] [Trazodone](#)

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

2) Summary: Both [amphetamine](#) 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](#) [38]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [amphetamine](#) and [trazodone](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [31].

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [amphetamine](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#) [38]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

### 3.5.1.BN] [Trimipramine](#)

- 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](#) [62] [63]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [64]. 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 [65]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [66]. 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 [53] [54] [2] [55]. 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 [53] [54] [2].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [56].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [57].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [58] [55].

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



weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [59].

**f)** There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [60]. 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 [61].

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

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

**2)** Summary: Two weeks of concurrent use of [dextroamphetamine](#) and [venlafaxine](#) resulted in symptoms of [serotonin syndrome](#) in a 32-year-old male [30]. If [dextroamphetamine](#) and [venlafaxine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [31].

**3)** Severity: major

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: A case of [serotonin syndrome](#) was reported with coadministration of [dextroamphetamine](#) and [venlafaxine](#) [30]. If [dextroamphetamine](#) and [venlafaxine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#) such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [31].

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

**8)** Literature Reports

**a)** A 32-year-old male on [dextroamphetamine](#) experienced [serotonin syndrome](#) approximately 2 weeks after starting [venlafaxine](#). He was on [dextroamphetamine](#) 5 mg three times daily for [attention deficit hyperactivity disorder](#). He started 75 mg a day of [venlafaxine](#) for 1 week then the dose was increased to 150 mg daily. Approximately 2 weeks after starting [venlafaxine](#) he experienced marked agitation, anxiety, shivering, and tremor. On admission he was alert and oriented. He experienced diaphoresis, shivering, and fine motor tremor. His heart rate was 140 beats per minute, blood pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No [nystagmus](#) or ocular clonus was noted. Pupils were 3 mm diameter and reactive. He had generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerking, and unilateral-tonic spasm of his orbicularis oris muscle. No abnormality was shown on ECG, except [sinus tachycardia](#) with a baseline tremor. [Dextroamphetamine](#) and [venlafaxine](#) were discontinued and [cyproheptadine](#) (up to a total of 32 mg over 3 hours) was administered. Symptoms resolved and he was discharged the following morning. [Dextroamphetamine](#) was restarted 3 days later. Four days later [citalopram](#) was started. Approximately 1 week later, he experienced similar symptoms as he did with [dextroamphetamine](#) and [venlafaxine](#). Agitation, nausea, diarrhea, and teeth clenching were still present 3 days after [citalopram](#) was discontinued. Two doses of [cyproheptadine](#) were given and within 2 days he was asymptomatic [30].



**3.5.1.BP] Vilazodone**

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

2J) Summary: [Serotonin syndrome](#) has been reported with vilazodone monotherapy and in combination with other serotonergic drugs; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#) [89]. Increased serotonin levels which may produce additive serotonergic effects can occur if serotonergic agents are taken concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening [31]. Therefore, exercise caution with concomitant use of vilazodone and this drug. Monitor for [serotonin syndrome](#) and discontinue use of both vilazodone and the concomitant serotonergic agent immediately if symptoms of [serotonin syndrome](#) emerge [89].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Serotonin syndrome](#) has been reported with vilazodone monotherapy and in combination with other serotonergic drugs; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use and monitor for [serotonin syndrome](#). Discontinue use of vilazodone and concomitant serotonergic agents immediately if symptoms of [serotonin syndrome](#) emerge [89].

7J) Probable Mechanism: additive serotonergic effects

**3.5.1.BQ] Vortioxetine**

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

2J) Summary: Vortioxetine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with caution. [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy [126].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of vortioxetine with serotonergic agents may increase the risk for [serotonin syndrome](#) and should be undertaken with caution. If concomitant use of vortioxetine with a serotonergic agent is clinically warranted, close monitoring of the patient is recommended, particularly during treatment initiation and dosage increases. If [serotonin syndrome](#) develops, discontinue vortioxetine and concomitant serotonergic agents and initiate supportive care [126].

7J) Probable Mechanism: additive serotonergic effects

**3.5.1.BR] Ziprasidone**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [36] [37]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [36] [37]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.2] Drug-Food Combinations

#### 3.5.2.A] Acidic Food

- 1) Interaction Effect: altered serum concentrations
- 2) Summary: Maximal absorption of [amphetamines](#) occurs in the alkaline environment of the small intestine [222]. Acidic fruits or juices taken with [amphetamines](#) may impair gastrointestinal absorption. Foods that increase urinary pH may decrease renal clearance, resulting in renal reabsorption of the [amphetamine](#) and increased serum levels. Foods that acidify urine increase renal clearance of [amphetamines](#) and may lower serum levels [223] [224].
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: [Dextroamphetamine](#) should not be administered with acidic foods, such as citric fruits and juices.
- 7) Probable Mechanism: pH-dependent absorption and clearance

## 4.0] Clinical Applications

[Monitoring Parameters](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

### 4.1] Monitoring Parameters

#### A) Therapeutic

##### 1) Physical Findings

###### a) ADHD

- 1) Improvement in mental and behavioral symptoms of ADHD, including inappropriate inattention, impulsivity, hyperactivity, and cognitive performance, is indicative of efficacy.
- 2) Reevaluate patient periodically for long-term usefulness of the drug by temporarily withdrawing therapy and monitoring for recurrence of behavioral symptoms and their severity [8] [9].

**b) Narcolepsy**

**1) Decreased frequency of narcoleptic attacks is indicative of efficacy (Adderall(R)).**

**B) Toxic****1) Physical Findings**

**a)** Evaluate blood pressure and heart rate for increases that are larger than average (ie, increases greater than 2 to 4 mmHg and 3 to 6 beats/min, respectively), especially in patients with [hypertension](#) and other cardiovascular conditions (eg, [heart failure](#), recent [myocardial infarction](#), or [ventricular arrhythmia](#)) [8] [9] with routine follow-up within 1 to 3 months, and at follow-up visits every 6 to 12 months [228] [229].

**b)** Assess cardiovascular status prior to and during treatment (ie, patient history for family history of sudden death or [ventricular arrhythmia](#) and physical exam for presence of cardiac disease), perform further cardiac evaluation (eg, ECG and [echocardiogram](#)) if indicated [8] [9].

**c)** The American Academy of Pediatrics (AAP) does not recommend the routine use of ECGs or routine subspecialty cardiology evaluations (which were previously recommended by the American Heart Association (AHA) scientific statement [228] [229] to detect cardiac conditions that might place the child at risk for sudden cardiac death [SCD]) before initiating stimulant therapy to treat 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 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 [228]. Based on the AAP and the AHA consensus statements, the following cardiac monitoring recommendations have been established to assist clinicians in the evaluation of children treated with stimulant drugs for ADHD [228] [229]:

- Conduct a thorough examination prior to initiating stimulant 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 sudden cardiac death (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.
- 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, during routine follow-up within 1 to 3 months, and at follow-up visits every 6 to 12 months. Increases in blood pressure and heart rate have been reported with stimulant use.

**d)** Screen ADHD patients for [bipolar disorder](#) risk factors (ie, detailed psychiatric history, including family history of suicide, [bipolar disorder](#), and depression) prior to treatment [8] [9].

e) Monitor pediatric patients for new onset or worsening aggressive behavior or hostility at the start of treatment [8] [9].

f) Monitor growth in pediatric patients [8] [9].

g) Observe for digital changes (eg, peripheral vasculopathy, including [Raynaud's phenomenon](#)) during ADHD treatment and if needed, conduct further evaluation (eg, rheumatology referral) [8].

h) Evaluate for tics and [Tourette's syndrome](#), especially in pediatrics and their families, prior to treatment [8] [9].

#### 4.3] Place In Therapy

A) There is a high potential for abuse and prolonged administration may lead to dependence. Misuse has been associated with sudden death and serious cardiovascular adverse events. The effectiveness of long-term use has not been systematically evaluated in controlled trials. Therefore, use for extended periods should be periodically reevaluated [19] [9].

#### B) [Attention Deficit Hyperactivity Disorder](#)

1) [Dextroamphetamine](#) sulfate/[dextroamphetamine](#) saccharate/[amphetamine](#) sulfate/[amphetamine](#) aspartate is indicated for the treatment of ADHD in patients 3 years or older (immediate-release tablets), or 6 years or older (extended-release capsules). Therapy should be an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome [19] [9]. Long-term use, for more than 3 weeks in children and 4 weeks in adolescents and adults, has not been systematically evaluated in controlled trials. If possible, therapy should be interrupted occasionally to determine the need for continued therapy [19].

#### C) [Narcolepsy](#)

1) The immediate-release tablet formulation of [dextroamphetamine](#) sulfate/[dextroamphetamine](#) saccharate/[amphetamine](#) sulfate/[amphetamine](#) aspartate is indicated in patients 6 years or older for the treatment of [narcolepsy](#). Use for extended periods should be periodically reevaluated [9].

#### 4.4] Mechanism of Action / Pharmacology

A) [Amphetamines](#) are noncatechol sympathetic amines with CNS stimulant activity. The mechanism of therapeutic activity in ADHD is not known. [Amphetamines](#) are purported to block the reuptake of [norepinephrine](#) and [dopamine](#) into the presynaptic neuron, and increase their release into the extraneuronal space [227].

#### 4.5] Therapeutic Uses

##### 4.5.A] [Attention deficit hyperactivity disorder](#)

##### FDA Labeled Indication

##### 1) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(immediate-release, age 3 years and older; extended-release, age 6 years and older\)](#)

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**2) Summary:**

[Dextroamphetamine sulfate/dextroamphetamine saccharate/amphetamine sulfate/amphetamine aspartate](#) as combination therapy is indicated for the treatment of [attention deficit hyperactivity disorder](#) (ADHD) [1]

**3) Adult:**

**a)** Adderall(R), a mixture of L- and D-amphetamine, was effective in some cases of adult attention deficit hyperactive disorder, based on a pilot open-label study (n=24). Dosing of Adderall was initiated at 5 milligrams (mg) twice daily orally and titrated according to response. By the end of 16 weeks of treatment, a positive response was shown by 54% of patients (13 of 24) using the Clinical Global Impression scale to define progress; 10 patients (42%) were very much improved and 3 (12%) were much improved. Two patients (8%) were minimally improved. Among these responders (n=15), mean daily dose was 10.33 mg or 0.14 mg/kg/day, and side effects were decreased appetite, insomnia, and sedation. Overall, 9 patients (38%) were poor- or nonresponders. Four of 7 with comorbid anxiety experienced immediate acute anxiety (diaphoresis, tremor, shortness of breath, and sense of impending doom), and dropped out after day 1. Excluding those 4, mean score on the Copeland [Symptom Checklist](#) for adult ADD decreased from 99.05 to 63.3, and mean score on the Brown ADD scales dropped from 76.75 to 50.85 (p less than 0.001 and 0.0001, respectively) (Horrigan and Barnhill, 2000).

**4) Pediatric:**

**a) Extended-Release**

**1)** In a double-blind, randomized, placebo-controlled, parallel-group study, extended release Adderall (Adderall XR(TM)) was safe and effective for the treatment of [attention deficit hyperactivity disorder](#) (ADHD) in children ages 6 to 12 years old. Patients (n=584) who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for hyperactive-impulsive or combined subtypes of ADHD were randomized to either placebo (n=210), or 10 milligrams per day (mg/day; n=129), 20 mg/day (n=121), or 30 mg/day (n=124) Adderall XR(TM). All patients received placebo for a 1-week washout period. Once active treatment began, a dose escalation regimen was used for the Adderall XR (TM) groups; a starting oral dose of 10 mg once daily was administered to all Adderall XR(TM) groups and increased each week by 10 mg per day until the assigned dose was reached. Efficacy was evaluated using the Conners Global Index Scale (teacher's version, CGIS-T or parent's version, CGIS-P) in the morning and afternoon. All Adderall XR (TM) groups showed significant improvement in CGIS scores compared to baseline and placebo (p less than 0.001). Mean baseline CGIS-T scores were 10.6, 11.5, 12.1, and 11.2 for the placebo, 10 mg/d, 20 mg/d, and 30 mg/day groups, respectively. The average change in CGIS-T score at study endpoint was -0.9, -5.3, -6.0, and -6.4, respectively. Adverse events that occurred more frequently in the treatment groups than in the placebo group were anorexia (21.9% in Adderall XR(TM) groups versus 1.9% in placebo), insomnia (16.6% versus 1.9%), abdominal pain (14.4% versus 9.5%), emotional lability (8.6% versus 1.9%), vomiting (7.2% versus 3.8%), and nervousness (5.6% versus 1.9%). Fifteen patients (6 placebo, 9 treatment) were withdrawn from the study due to adverse events [3].

**b) Immediate-Release**

1J) Seven-day courses of oral Adderall(R) (a mixture of **DEXTROAMPHETAMINE** AND **AMPHETAMINE** salts) at doses of 0.15 milligram/kilogram (mg/kg) and 0.3 mg/kg, both twice daily, were found to be an efficacious treatment for attention-deficit/hyperactive disorder (DSM-IV) in children and adolescents 5 to 18 years of age, based on a randomized, double-blind, crossover study. A 54% response rate to Adderall(R) was seen based on strict criteria requiring positive assessments seen by both parent and teacher, 81% were seen to respond as rated by parents, and 73% responded according to teachers. Overall, 137 of 154 subjects (89%) responded based on either parent or teacher positive evaluation. Using the strict criteria (positive ratings by parent and teacher), 60% of children 5 to 7 years of age responded; 71% of those 8 to 9 years responded, as did 48% of children 10 years of age and older. Side effects of Adderall(R) included decreased appetite, stomachache, insomnia, and headache; decreased appetite and insomnia were more prominent with the 0.3 mg/kg dose. According to the study design, subjects were randomized to start on either Adderall(R) or placebo. There were four 7-day treatment periods (Adderall(R), placebo, Adderall(R), placebo; or vice versa starting with placebo). Because the half-life of Adderall(R) is 4 to 8 hours, a washout period between the 7-day treatment periods was not thought to be necessary. The lower Adderall(R) dose was given before the higher dose, with a maximum Adderall(R) dose of 40 mg/day [4].

#### 4.5.BJ Narcolepsy

##### FDA Labeled Indication

##### 1J) Overview

FDA Approval: Adult, yes (immediate release formulation only); **Pediatric, yes ((6 years and older) immediate release formulation only)**

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

##### 2J) Summary:

**Dextroamphetamine** sulfate/**dextroamphetamine** saccharate/**amphetamine** sulfate/**amphetamine** aspartate as combination therapy is indicated for the treatment of **narcolepsy** [1]

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