

DRUGDEX-EV 0442

MICROMEDEX

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## DEXTROAMPHETAMINE

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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) [Dextroamphetamine Sulfate](#)

##### 1] Adult

a) [Narcolepsy](#)

1) immediate-release, 5 to 60 mg ORALLY in 2 to 3 divided doses daily [1]

2) sustained-release, 5 to 60 mg ORALLY as single daily dose [2]

##### 2] Pediatric

a) (immediate-release) **not FDA approved for children under 3 yr of age** with [attention deficit hyperactivity disorder](#) [27]

b) (sustained-release) not FDA approved for children under 6 yr of age with [attention deficit hyperactivity disorder](#) [2]

##### 1] Attention deficit hyperactivity disorder

a) (immediate-release, age 3 to 5 yr) initial, 2.5 mg ORALLY once daily, increase by 2.5 mg/day at 1 wk intervals to optimum response; MAX 40 mg/day [1]

**b))** (immediate-release, age 6 yr and older) initial, 5 mg ORALLY once or twice daily, increase by 5 mg at 1 wk intervals to optimum response; MAX 40 mg/day [1]

**c))** (sustained-release, age 6 yr and older) initial, 5 mg ORALLY once or twice daily, increase by 5-mg mg/day at 1 wk intervals to optimum response; MAX 40 mg/day [2]

## **2)) Narcolepsy**

**a))** (age 6 to 12 yr) 5 mg/day ORALLY, increase by 5 mg/day at 1 wk intervals to optimum response; MAX 40 mg/day; sustained-release tablets should be dosed once daily, immediate-release doses may be given at intervals of 4 to 6 hours [1][2]

**b))** (age 12 yr and older) 10 mg/day ORALLY, increase by 10 mg/day at 1 wk intervals to optimum response; MAX 40 mg/day; sustained-release tablets should be dosed once daily, immediate-release doses may be given at intervals of 4 to 6 hours [1][2]

## **3)) Contraindications**

### **a)) Dextroamphetamine Sulfate**

**1))** agitated states [28]

**2))** [arteriosclerosis](#), advanced [28]

**3))** [cardiovascular disease](#), symptomatic [28]

**4))** drug dependence, history [28]

**5))** [glaucoma](#) [28]

**6))** hypersensitivity/idiosyncrasy to sympathomimetic amines or [amphetamine](#) [29]

**7))** [hypertension](#), moderate to severe [28]

**8))** [hyperthyroidism](#) [28]

**9))** MAOI use, including [linezolid](#) or methylene blue; concomitantly or within 14 days of administration; [hypertensive crisis](#) may occur [29]

## **4)) Serious Adverse Effects**

### **a)) Dextroamphetamine Sulfate**

**1))** Aggressive behavior

**2))** Cerebrovascular accident

- 3j) Decreased body growth
- 4j) Drug dependence
- 5j) Increased heart rate
- 6j) [Intracranial hemorrhage](#)
- 7j) Lowered convulsive threshold
- 8j) [Myocardial infarction](#)
- 9j) [Peripheral vascular disease](#)
- 10j) [Psychotic disorder](#)
- 11j) [Raynaud's disease](#)
- 12j) Sudden cardiac death

## 5j) Clinical Applications

### a) [Dextroamphetamine Sulfate](#)

#### 1j) FDA Approved Indications

- a) [Attention deficit hyperactivity disorder](#)
- b) [Narcolepsy](#)

## 1.0j Dosing Information

[Drug Properties](#)

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### 1.1j Drug Properties

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

**Bj)** Synonyms

D-Amphetamine  
 Dexamfetamine  
 Dexamfetamine Sulfate  
 Dexamphetamine  
 Dexamphetamine Sulfate  
[Dextroamphetamine](#)  
[Dextroamphetamine Sulf](#)  
[Dextroamphetamine Sulfate](#)

### 1.2j Storage and Stability

**A) Dextroamphetamine Sulfate****1) Preparation****a) Oral route**

**1) Avoid late evening doses due to resulting insomnia [2][27]**

**2) Give first dose of immediate-release tablet on awakening, and additional doses at intervals of 4 to 6 hours [27].**

**B) Oral route**

**1) Dextroamphetamine** tablets should be stored in well-closed containers, and the elixir in tight, light-resistant containers, at a temperature of less than 40 degrees Centigrade, preferably at 15 to 30 degrees Centigrade (59 to 86 degrees F); freezing of the elixir should be avoided. The extended-release capsules should be stored at temperature, between 20 and 25 degrees C (68 and 77 degrees F) [94][95].

**1.3] Adult Dosage****1.3.1] Normal Dosage****1.3.1.A] Dextroamphetamine Sulfate****1.3.1.A.1] Narcolepsy**

See Drug Consult reference: [Narcolepsy](#) and [Cataplexy](#) - Drug Therapy

**1.4] Pediatric Dosage****1.4.1] Normal Dosage****1.4.1.A] Dextroamphetamine Sulfate****1.4.1.A.1] Oral route****1.4.1.A.1.a] Attention deficit hyperactivity disorder****1) Immediate-Release**

**a) For children 3 to 5 years of age with attention deficit disorder**, the recommended initial oral dose of **dextroamphetamine** is 2.5 milligrams/day. The daily dosage is increased by 2.5 milligrams at weekly intervals until the optimum response is attained. The total daily dose should rarely exceed 40 milligrams. The first dose should be given on awakening if tablets or liquid are used, with subsequent doses spaced at intervals of 4 to 6 hours [1].

**b) For children 6 years of age and older with attention deficit disorder**, the recommended initial dose of oral **dextroamphetamine** is 5 milligrams once or twice daily. The daily dosage is increased by 5 milligrams at weekly intervals until the optimum response is attained. Rarely should the total daily dose exceed 40 milligrams. The first dose should be given on awakening, with subsequent doses spaced at intervals of 4 to 6 hours [1].

**2) Extended-Release**

a) For children aged 6 years and older with [attention deficit disorder](#), the recommended initial dose of oral [dextroamphetamine](#) sustained-release is 5 milligrams (mg) once or twice daily, with 5-mg increases at weekly intervals until the optimum dose is attained. Exceeding a total daily dose of 40 mg is rarely necessary [2].

#### 1.4.1.A.1.b) [Narcolepsy](#)

##### 1) Immediate-release

a) For children 6 to 12 years of age with [narcolepsy](#), the recommended initial dose of oral [dextroamphetamine](#) immediate-release is 5 milligrams (mg) daily, with 5-mg increases at weekly intervals until the optimum dose is attained [1].

b) For children 12 years of age and older with [narcolepsy](#), the initial dose of oral [dextroamphetamine](#) immediate-release is 10 mg daily, with 10-mg increases at weekly intervals until the optimum dose is attained. The first dose should be given on awakening, with subsequent doses (1 or 2) spaced at intervals of 4 to 6 hours. Exceeding a total dose of 40 mg/day is rarely necessary. Occasional interruption of therapy is recommended to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy [1].

##### 2) Sustained-release

a) For children 6 to 12 years of age with [narcolepsy](#), the recommended initial dose of oral [dextroamphetamine](#) sustained-release is 5 milligrams (mg) once daily, with 5-mg increases at weekly intervals until the optimum dose is attained [2].

b) For children 12 years of age and older with [narcolepsy](#), the recommended initial dose of oral [dextroamphetamine](#) sustained-release is 10 mg once daily, with 10-mg increases at weekly intervals until the optimum dose is attained [2].

c) Dosage should be reduced if adverse reactions become intolerable [2].

## 2.0] Pharmacokinetics

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

### 2.1] Onset and Duration

#### A) Duration

##### 1) [Dextroamphetamine](#) Sulfate

##### a) Single Dose

1) 4 to 24 hours (Johnson et al, 1971).

a) The duration of the effects may be prolonged by alkalinization or shortened by acidification of the urine [86].

b) Each dextroamphetamine sustained-release capsule is prepared such that an initial dose is promptly released; the remaining medication is then released

gradually over a prolonged period of time. Dextroamphetamine's therapeutic effects may persist for 24 hours [86].

## 2.2] Drug Concentration Levels

### A) [Dextroamphetamine](#) Sulfate

#### 1) Peak Concentration

a) Immediate-release tablets, oral, single dose, 15 mg: 36.6 nanograms/mL [87]

1) The C<sub>max</sub> of dextroamphetamine was 36.6 nanograms/mL following a single 15-mg dose of immediate-release tablets (3 x 5 mg tablets) to 12 healthy subjects [87].

b) Sustained-release capsule, oral, single dose, 15 mg: 23.5 nanograms/mL [53]

1) The C<sub>max</sub> of dextroamphetamine was 23.5 nanograms/mL following a single 15-mg dose of a sustained-release capsule to 12 healthy subjects [53].

#### 2) Time to Peak Concentration

a) Immediate-release tablet, oral: 3 hours [87]

1) The T<sub>max</sub> of dextroamphetamine was 3 hours following a single 15-mg dose of immediate-release tablets (3 x 5 mg tablets) to 12 healthy subjects [87].

b) Sustained-release capsule, oral: 8 hours [53]

1) The T<sub>max</sub> of dextroamphetamine was 8 hours following a single 15-mg dose of a sustained-release capsule to 12 healthy subjects [53].

## 2.3] ADME

### 2.3.1] Absorption

#### A) [Dextroamphetamine](#) Sulfate

##### 1) Effects of Food

a) None (sustained-release capsule) [53]

1) There was no significant effect on the rate or extent of dextroamphetamine absorption following administration of a sustained-release capsule in a fed state (58 to 75 g fat) compared with a fasted state in 12 healthy subjects [53].

### 2.3.2] Distribution

**A) Distribution Sites**

**1) Dextroamphetamine Sulfate**

**a) Tissues and Fluids**

**1) Cerebrospinal fluid**

**a)** Cerebrospinal fluid levels of dextroamphetamine are approximately 80% of plasma levels [88].

**2) Hair**

**a)** The Vd of dextroamphetamine in the hair of 40 healthy adults receiving 10 mg orally daily for 7 days was 17.7 mg and the absorption rate constant from plasma into hair was 1.6E(-6)/hr [89].

**B) Distribution Kinetics**

**1) Dextroamphetamine Sulfate**

**a) Volume of Distribution**

**1)** 6.11 L/kg [88].

**2.3.3] Metabolism**

**A) Metabolism Sites and Kinetics**

**1) Dextroamphetamine Sulfate**

**a)** Liver, extensive [90][91][86][92]

**1)** Amphetamine is hepatically metabolized to both acidic and basic metabolites primarily by deamination and hydroxylation [90][91][86][92]. Dextroamphetamine is the dextrorotatory isomer of amphetamine and would be expected to behave in a similar fashion.

**B) Metabolites**

**1) Dextroamphetamine Sulfate**

**a)** Hippuric acid (Davies et al, 1971)[91][86][93].

**b)** Benzoic acid (Davies et al, 1971)[91][86][93].

**c)** Norephedrine (Davies et al, 1971)[91][86][93].

**d)** 4-hydroxynorephedrine (Davies et al, 1971)[91][86][93].

e) Benzyl methyl ketone (Davies et al, 1971)[91][86][93].

### 2.3.4] Excretion

#### A) Kidney

##### 1) [Dextroamphetamine Sulfate](#)

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

1) 17% to 73% [86].

a) The urinary excretion of dextroamphetamine is dependent on pH; at a pH of less than 6.6, 67% to 73% of unchanged drug is excreted in the urine [86][91][92]. At a urine pH of greater than 6.7, 17% to 43% is excreted unchanged in the urine [86].

### 2.3.5] Elimination Half-life

#### A) Parent Compound

##### 1) [Dextroamphetamine Sulfate](#)

a) 12 hours [53][87]

1) The  $t(1/2)$  of dextroamphetamine was about 12 hours and was similar with immediate-release tablets and sustained-release capsules [53][87]

### 2.3.6] Extracorporeal Elimination

#### A) [Hemodialysis](#)

##### 1) [Dextroamphetamine Sulfate](#)

a) Dialyzable: There is inadequate experience to make a recommendation for [hemodialysis](#) of [dextroamphetamine](#) overdose[53][87]

#### B) Peritoneal

##### 1) [Dextroamphetamine Sulfate](#)

a) Dialyzable: There is inadequate experience to make a recommendation for [peritoneal dialysis](#) of [dextroamphetamine](#) overdose[53][87]

## 3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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



## Drug Interactions

### 3.0.A] Black Box WARNING

#### Dextroamphetamine Sulfate

##### Oral (Capsule, Extended Release)

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence and must be avoided. Particular attention should be paid 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 amphetamines may cause sudden death and serious cardiovascular adverse events [28].

### 3.1] Contraindications

#### A) Dextroamphetamine Sulfate

- 1) agitated states [28]
- 2) [arteriosclerosis](#), advanced [28]
- 3) [cardiovascular disease](#), symptomatic [28]
- 4) drug dependence, history [28]
- 5) [glaucoma](#) [28]
- 6) hypersensitivity/idiosyncrasy to sympathomimetic amines or [amphetamine](#) [29]
- 7) [hypertension](#), moderate to severe [28]
- 8) [hyperthyroidism](#) [28]
- 9) MAOI use, including [linezolid](#) or methylene blue; concomitantly or within 14 days of administration; [hypertensive crisis](#) may occur [29]

### 3.2] Precautions

#### A) Dextroamphetamine Sulfate

- 1) abuse and dependence; this drug has a high potential for abuse and dependence [28]
- 2) [amphetamine](#) misuse; may cause sudden death and serious cardiovascular events [28]
- 3) aggressive behavior and hostility have been reported; monitoring recommended [28]
- 4) [bipolar disorder](#), comorbid; may precipitate a mixed/[manic episode](#) [28]
- 5) blood pressure and heart rate increases have been reported; may impact underlying medical conditions such as preexisting [hypertension](#), [heart failure](#), recent [myocardial infarction](#), ventricular [arrhythmia](#), or [hyperthyroidism](#); monitoring recommended [28]

- 6j) cardiac abnormalities (structural), [cardiomyopathy](#), serious heart rhythm abnormalities, or other serious cardiac problems; sudden death has been reported with CNS stimulant treatment; avoid use [28]
- 7j) growth suppression may occur with consistent, long-term use; monitoring recommended; treatment interruption may be necessary [28]
- 8j) [myocardial infarction](#), [stroke](#), and death have been reported with stimulant treatment at usual doses in adults [28]
- 9j) peripheral vasculopathy (eg, [Raynaud's phenomenon](#)) has been reported; digital [ulceration](#) and/or soft tissue breakdown may result; monitoring recommended; dosage adjustment or discontinuation may be necessary [28]
- 10j) [psychosis](#), comorbid; may exacerbate symptoms of behavior disturbance and thought disorder [28]
- 11j) psychotic or manic symptoms (eg, hallucinations, delusional thinking, or mania) may occur in children or adolescents with no prior history of psychotic illness or mania at usual doses; discontinuation may be necessary [28]
- 12j) seizures may occur; may lower convulsive threshold, particularly in patients with seizure history or EEG abnormalities; discontinuation required [28]
- 13j) [serotonin syndrome](#) may occur, especially with concurrent use with other serotonergic drugs (eg, MAOIs (including IV methylene blue and [linezolid](#)), SSRIs, serotonin [norepinephrine](#) reuptake inhibitors, triptans, tricyclic antidepressants, [fentanyl](#), [lithium](#), [tramadol](#), tryptophan, [buspirone](#), St John's wort), or CYP2D6 inhibitors that may increase [dextroamphetamine](#) exposure; reduce dosage if concomitant use is necessary. Monitoring recommended; immediately discontinue both agents if symptoms occur [29].
- 14j) tics, motor and phonic, in children, personal or family history; risk of exacerbation [28]
- 15j) [Tourette syndrome](#) in children, personal or family history; risk of exacerbation [28]
- 16j) vision disturbances (ie, accommodation difficulties, blurred vision) have been reported with stimulant treatment [28]

### 3.3] Adverse Reactions

#### 3.3.1] Cardiovascular Effects

##### 3.3.1.A] [Dextroamphetamine Sulfate](#)

###### 3.3.1.A.1] [Cardiomyopathy](#)

- a) Isolated reports of [cardiomyopathy](#) have been associated with chronic use of [amphetamine](#) [28].

###### 3.3.1.A.2] [Increased blood pressure](#)

- a) Palpitations, [tachycardia](#), and increases in blood pressure have been reported during [dextroamphetamine](#) therapy, including isolated reports of [cardiomyopathy](#) associated with chronic use. Use [dextroamphetamine](#) cautiously in patients whose underlying medical conditions (such as preexisting [hypertension](#), [heart failure](#), or recent [myocardial infarction](#)) may be compromised with increases in blood pressure [28].

### 3.3.1.A.3] Increased heart rate

a)] CNS stimulants cause a mean increase in heart rate of 3 to 6 beats per minute; monitoring for [tachycardia](#) is recommended in all patients. Use [dextroamphetamine](#) cautiously in patients whose underlying medical conditions (such as preexisting [hypertension](#), [heart failure](#), or recent [myocardial infarction](#)) may be compromised with increases in heart rate. Palpitations, [tachycardia](#), and increases in blood pressure have also been reported during [dextroamphetamine](#) therapy, including isolated reports of [cardiomyopathy](#) associated with chronic use [28].

b)] Increases in heart rate and blood pressure were reported with use of [dextroamphetamine](#). In a placebo-controlled, crossover study of cardiovascular effects, [dextroamphetamine](#) 30 mg in 3 divided doses (midnight, 0400 hours, and 0800 hours) was administered to male (n=6) and female (n=6) military pilots during sleep-deprivation periods. Heart rates were elevated from 2 hours after the second 10-mg dose until 14 hours after the third dose. In females, average heart rates associated with [dextroamphetamine](#) and placebo were 84 and 71 beats per minute (bpm), respectively; in males, these rates were 70 and 63 bpm, respectively. Systolic blood pressure (SBP) in males was elevated from 1 hour after the first 10-mg dose until 5 hours after the third dose; SBP in females was increased 1 hour after the third 10-mg dose and remained high 5 hours thereafter. Diastolic blood pressure (DBP) was elevated from 2 hours after the second dose and continued for 6 hours after the last dose in both genders. Mean SBP after [dextroamphetamine](#) and placebo was 128 and 120 mmHg, respectively, and DBP was 72 and 69 mmHg for [dextroamphetamine](#) and placebo, respectively [36].

### 3.3.1.A.4] Myocardial infarction

#### a)] Adults

1)] [Myocardial infarction](#) has been reported in adults being treated with CNS stimulant drugs at usual doses [28].

#### b)] Children and Adolescents

1)] 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) [33]. 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 children and young adults studied. Patients with serious heart problems or for whom an increase in blood pressure or heart rate would be problematic should not be prescribed stimulant medications. Monitoring for changes in heart rate or blood pressure is recommended in all patients [34].

### 3.3.1.A.5] Palpitations

a)] Palpitations, [tachycardia](#), and increases in blood pressure have been reported during [dextroamphetamine](#) therapy, including isolated reports of [cardiomyopathy](#) associated with chronic use [28].

### 3.3.1.A.6] Peripheral vascular disease

a) Effects of peripheral vasculopathy, including [Raynaud's phenomenon](#), were reported with postmarketing use of stimulants, including [dextroamphetamine](#) sulfate, at therapeutic doses. 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 [28].

#### 3.3.1.A.7] [Raynaud's disease](#)

a) Effects of peripheral vasculopathy, including [Raynaud's phenomenon](#), were reported with postmarketing use of stimulants, including [dextroamphetamine](#) sulfate, at therapeutic doses. 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 [28].

#### 3.3.1.A.8] Sudden cardiac death

##### a) Summary

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of [electrocardiograms](#) (ECGs) or routine subspecialty cardiology evaluations (which were previously recommended by the American Heart Association (AHA) scientific statement to detect cardiac conditions that might place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity disorder (ADHD) in most children. The APA cited specific reasons for this change, including lack of evidence establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher than that in the general population of children, and lack of cost-effective analysis to support ECG screening or special evaluation by pediatric cardiologist [31]. 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, including [dextroamphetamine](#), for ADHD [31][32]:

Conduct a thorough examination prior to initiating [dextroamphetamine](#) therapy for a diagnosis of ADHD. Special attention should be given to symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.

Obtain a complete family and patient history for conditions associated with SCD, and determine current use of any other prescription or over-the-counter medications. Conduct a complete physical evaluation of the patient for [hypertension](#), cardiac murmurs, physical findings associated with [Marfan syndrome](#), and signs of irregular cardiac rhythms.

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.

##### b) Adults

1)) Sudden death has been reported in adults being treated with CNS stimulant drugs at usual doses [28]

c) Children and Adolescents

1) Following administration of CNS stimulant drugs at usual doses, sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious heart problems who were treated for ADHD at recommended dosages [28].

2) 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 drugs (methylphenidate, dextromethylphenidate, dextroamphetamine, amphetamine salts, atomoxetine, or pemoline) compared with those who did not (adjusted hazard ratio, 0.75; 95% CI, 0.31 to 1.85) [33]. 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 children and young adults studied. Patients with serious heart problems or for whom an increase in blood pressure or heart rate would be problematic should not be prescribed stimulant medications. Monitoring for changes in heart rate or blood pressure is recommended in all patients [34].

3) A retrospective, case-controlled study examined the association between stimulant medication, including dextroamphetamine sulfate, 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 youngsters who died as passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youths 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 [35].

### 3.3.1.A.9) Summary

a) Sudden death, stroke, and myocardial infarction have been reported in patients taking usual doses of stimulant drugs [28]. Large cohort studies have shown there is no significant difference in the incidence of serious cardiovascular events (sudden death, stroke, and acute myocardial infarction) in both children [33] and adults [37] currently receiving stimulant medications compared with nonusers, however a slight to modest increase in risk cannot be ruled out. Patients with serious heart problems or those in whom an increase in blood pressure or heart rate would be problematic, should not be prescribed stimulant medications. Perform a thorough history to determine if there is a family history of sudden death or ventricular arrhythmia and a physical exam to assess the existence of cardiac disease prior to prescribing these drugs to patients. Periodic monitoring for changes in heart rate or blood pressure is recommended in all patients taking stimulant medications [34].

### 3.3.2] Dermatologic Effects

#### 3.3.2.A] **Dextroamphetamine Sulfate**

##### 3.3.2.A.1] **Urticaria**

- a) **Urticaria** has been reported with **dextroamphetamine** therapy [28].

### 3.3.3] Endocrine/Metabolic Effects

#### 3.3.3.A] **Dextroamphetamine Sulfate**

##### 3.3.3.A.1] **Decreased body growth**

- a) Summary

1) It is unknown if chronic use of stimulants, including **dextroamphetamine**, in children may cause suppression of growth. However, 1 study identified temporary growth suppression with consistent **methylphenidate** use (ie, treatment for 7 days per week throughout the year). It is anticipated that chronic use of **amphetamines** will have this effect as well and therefore growth should be monitored during treatment with **dextroamphetamine**. Treatment interruption may be necessary for patients who are not growing or gaining weight as expected [28].

b) One study compared the growth of 63 hyperactive children of which 29 received **dextroamphetamine** (median, 12.5 mg/day), 20 received **methylphenidate** (median, 20 mg/day) and 14 received no medication. Height measurements were retrieved annually over a period of 2 or more years from student health records. Long-term administration of **dextroamphetamine** and **methylphenidate** demonstrated a statistically significant inhibition of growth when compared with the control group; however, when the mean percentile loss was extrapolated to annual lag in height in centimeters (cm), growth suppression was only minimal, 1.5 and 1 cm/year, respectively. Growth inhibition was only noticeable with **methylphenidate** doses greater than 20 mg/day [51]. A follow-up study demonstrated that rebound growth occurred upon discontinuing the CNS stimulant during the summer months [52].

##### 3.3.3.A.2] **Hyperthyroidism**

a) One group of clinicians reports 4 cases of **amphetamine abuse** that resulted in an elevated free thyroxine index, elevated T3 and T4 levels, and signs and symptoms of **hyperthyroidism**. The levels of T4 appeared to be inappropriately elevated compared to T3 levels. The **hyperthyroxinemia** appeared to be secondary to an increase in circulating **TSH**. All levels returned to normal after the discontinuation of **amphetamine** in 2 of the 4 cases; the remaining 2 patients refused further follow-up after the initial levels were obtained (Morely et al, 1980). **Dextroamphetamine** is the dextrorotatory isomer of **amphetamine** and would be expected to behave in a similar fashion.

b) The signs and symptoms of **amphetamine abuse** are similar to those of **thyrotoxicosis**; it is uncertain which, if any, of these symptoms are secondary to **hyperthyroxinemia** (Morely et al, 1980).

##### 3.3.3.A.3] **Weight decreased**

- a) Anorexia and weight loss has been reported with **dextroamphetamine** therapy [28].

### 3.3.4] Gastrointestinal Effects

#### 3.3.4.A] **Dextroamphetamine Sulfate**

#### 3.3.4.A.1] Constipation

a) Constipation has been reported with [dextroamphetamine](#) therapy [28].

#### 3.3.4.A.2] Diarrhea

a) Diarrhea has been reported with [dextroamphetamine](#) therapy [28].

#### 3.3.4.A.3] Loss of appetite

a) Anorexia and weight loss has been reported with [dextroamphetamine](#) therapy [28].

#### 3.3.4.A.4] Unpleasant taste in mouth

a) Unpleasant taste has been reported with [dextroamphetamine](#) therapy [28].

#### 3.3.4.A.5] Xerostomia

a) Dryness of the mouth has been reported with [dextroamphetamine](#) therapy [28].

### 3.3.5] Hematologic Effects

#### 3.3.5.A] [Dextroamphetamine](#) Sulfate

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

a) One report describes a case of a 24-year-old white man who ingested 8 to 16 tablets/day of [amphetamine](#) for 2.5 years who subsequently developed [myeloblastic leukemia](#) that was heralded by weakness, sweating, calf pain, and fever. Despite chemotherapy, the patient's condition rapidly deteriorated into coma, [apnea](#), and death. A possible cause and effect relationship with chronic [amphetamine](#) ingestion was postulated since the drug possesses a benzene ring that has been known to cause hematologic effects. [Dextroamphetamine](#) is the dextrorotatory isomer of [amphetamine](#) and would be expected to behave in a similar fashion [30].

### 3.3.8] Musculoskeletal Effects

#### 3.3.8.A] [Dextroamphetamine](#) Sulfate

##### 3.3.8.A.1] [Rhabdomyolysis](#)

a) Combined Adult and Adolescent Clinical Trials

1) [Attention deficit hyperactivity disorder](#) (oral route): Has been reported [53]

### 3.3.9] Neurologic Effects

#### 3.3.9.A] [Dextroamphetamine](#) Sulfate

##### 3.3.9.A.1] Central nervous system stimulation, excessive

a) Overstimulation has been reported with [dextroamphetamine](#) therapy [28].

##### 3.3.9.A.2] Cerebrovascular accident



a) Sudden death, [stroke](#), and [myocardial infarction](#) have been reported in patients taking usual doses of stimulant drugs [28]. Four cases of [stroke](#) were reported in patients (29 to 45 years of age) thought to have abused [methamphetamine](#); 2 patients had intracranial hemorrhaging and 2 had cerebral ischemic infarctions [38].

b) Children and Adolescents

1) 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 drugs ([methylphenidate](#), [dexmethylphenidate](#), [dextroamphetamine](#), [amphetamine](#) salts, [atomoxetine](#), or [pemoline](#)) compared with those who did not (adjusted hazard ratio, 0.75; 95% confidence interval (CI), 0.31 to 1.85) [33]. 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 children and young adults studied. Patients with serious heart problems or for whom an increase in blood pressure or heart rate would be problematic should not be prescribed stimulant medications. Monitoring for changes in heart rate or blood pressure is recommended in all patients [34].

### 3.3.9.A.3] [Disturbance in speech](#)

a) Central nervous system (CNS) stimulants can increase the rate of speech and reduce the fine coordinate control at the same time. This may cause [dysphonia](#) and voice tremors [50].

### 3.3.9.A.4] [Dizziness](#)

a) Dizziness has been reported with [dextroamphetamine](#) therapy [28].

### 3.3.9.A.5] [Dyskinesia](#)

a) [Dyskinesia](#) has been reported with [dextroamphetamine](#) therapy [28].

### 3.3.9.A.6] [Extrapyramidal sign](#)

a) Chronic [amphetamine abuse](#) may induce extrapyramidal effects such as choreiform or athetoid movements, ataxia, and disturbances of gait that resemble the gait seen in [Huntington's chorea](#). The syndrome generally develops during [amphetamine abuse](#) but may also be seen during abstinence; however, the symptoms may persist for long periods of time. [Dopamine](#) receptor-blocking agents may be of use in reducing the symptoms [40][41]. [Dextroamphetamine](#) is the dextrorotatory isomer of [amphetamine](#) and would be expected to behave in a similar fashion.

### 3.3.9.A.7] [Gilles de la Tourette's syndrome](#)

a) [Tourette syndrome](#) has been reported with [dextroamphetamine](#) therapy [28].

b) [Tourette syndrome](#) may be precipitated with the use of stimulant medications in the treatment of [attention deficit disorders](#) in children. Early signs of [Tourette syndrome](#) are difficult to distinguish from the [attention deficit disorder](#) symptoms. Children may therefore be mistakenly treated with additional stimulant medications. Stimulants may exacerbate severe motor and phonic tics; discontinuation of the stimulants and the possible initiation of [haloperidol](#) therapy is often required. In patients diagnosed as having an [attention deficit disorder](#), a clinical evaluation for tics and [Tourette syndrome](#) in children and their families should precede the use of stimulant medication. The use of



[dextroamphetamine](#) is contraindicated in children with [Tourette syndrome](#) or tics. In children with no symptoms of [Tourette's syndrome](#) or tics but with a family history, stimulants should be used very cautiously. If tics emerge during [dextroamphetamine](#) therapy, the drug should be discontinued [43].

c) These authors present several cases of children with [attention deficit disorders](#) who experienced hyperactivity, attention difficulties, and in some cases, motor tic symptoms. The patients were placed on stimulant therapy and experienced exacerbation or development of tics or [Tourette syndrome](#). [Stimulant withdrawal](#) and [haloperidol](#) therapy controlled the motor and phonic symptoms [44].

d) Researchers reviewed the medication histories of 200 children with [Tourette syndrome](#). Forty-eight patients had received stimulant drugs: 42 [methylphenidate](#), 5 [dextroamphetamine](#), 13 [pemoline](#). Thirty-nine of the 48 (81%) patients received stimulants after the appearance of the tics. Of these, the stimulant drugs increased tics in 8 patients, caused no change in 22, and decreased tics in one patient. Concomitant [haloperidol](#) therapy resulted in no difference in the incidence or frequency of tics in 8 patients. The patients who developed tics with stimulant therapy showed a decrease in the incidence and frequency after discontinuation of the stimulant [45].

### 3.3.9.A.8] Headache

a) Headache has been reported with [dextroamphetamine](#) therapy [28].

### 3.3.9.A.9] Insomnia

a) Insomnia has been reported with [dextroamphetamine](#) therapy [28].

### 3.3.9.A.10] Intracranial hemorrhage

a) Investigators reported 4 cases of [intracranial hemorrhage](#) following oral or nasal use of [amphetamine](#) or related compounds. Two of these patients had abnormal appearing cerebral blood vessels on [angiography](#). Available data now indicate that [intracerebral hemorrhage](#) may also occur in patients who use these drugs for the first time and nonrecreationally [47].

b) One article reports a case of [intracranial hemorrhage](#) that occurred 3 hours after the ingestion of [amphetamine](#) 40 mg with a single can of beer. The admitting blood pressure was 210/120 (systolic/diastolic). No evidence of [aneurysm](#) or [arteriovenous malformation](#) was found on [CT scan](#) [48]. Others report [intracranial hypertension](#) in a chronic [amphetamine](#) abuser who was treated with [phenytoin](#) and [prednisone](#) without a residual neurologic deficit. [Dextroamphetamine](#) is the dextrorotatory isomer of [amphetamine](#) and would be expected to behave in a similar fashion [49].

### 3.3.9.A.11] Lowered convulsive threshold

a) Clinical evidence suggests stimulants may lower convulsive threshold in patients with a prior history of seizures, in patients with prior EEG abnormalities in the absence of a history of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. Discontinue [dextroamphetamine](#) if seizures develop [28].

b) Children with ADHD who have normal EEGs have minimal risk for seizures should they receive stimulant therapy for ADHD ([methylphenidate](#), [dextroamphetamine](#), or combination [amphetamine](#) and [dextroamphetamine](#) (Adderall(R))). However, children with epileptiform EEGs may have considerable risk for eventual seizure, although the occurrence of seizure may or may not be attributable to use of the stimulant. These conclusions were based on a study of 234 children without known [epilepsy](#) who were diagnosed with ADHD. All had EEGs prior to parental choosing of stimulant treatment or foregoing stimulant treatment for their children's ADHD. Overall, 36 children (15.4%) demonstrated epileptiform abnormalities compared with 198 with normal EEGs. Of the 36 with abnormalities, 30 received stimulant treatment for ADHD. Three of the 30 who received

stimulant therapy experienced seizures ( $p$  less than 0.03), including a 9-year-old girl, a 7-year-old boy, and a 6-year-old boy. The girl was treated uneventfully with [methylphenidate](#) for 12 months, then 2 months after withdrawal of [methylphenidate](#) experienced a 4-minute generalized tonic-clonic seizure. Her EEG had revealed a non-focal epileptiform abnormality. Of the 2 boys, the first experienced a 2-minute generalized tonic [clonic seizure](#) with focal onset 3 years after starting [methylphenidate](#). The second boy had an episode at 10 months after initiation of [methylphenidate](#); he was heard to fall and was unresponsive with upward eye deviation for 2 minutes. EEGs of both boys had shown rolandic spikes, a focal epileptiform abnormality. One child who had a normal EEG had a seizure 6 weeks after beginning [methylphenidate](#) [39].

### 3.3.9.A.12] Tic

#### a) Summary

- 1) Exacerbation of motor and phonic tics has been reported with [dextroamphetamine](#) therapy. A clinical evaluation for tics and [Tourette syndrome](#) in children and their families should precede the use of stimulant medication [28].
- b) The incidence of tics emergence was 7.8% in children treated with stimulant medication ([methylphenidate](#), [dextroamphetamine](#), or [pemoline](#)) for ADHD, based on a retrospective chart review ( $n=555$ ). These stimulant medications were initiated only in children if they were free of tics and without a history of tics according to the practice of the settings in which the study was performed. Tics developed in 8.3% of subjects treated with [methylphenidate](#), 6.3% treated with [dextroamphetamine](#), and 7.7% treated with [pemoline](#). Onset of tics was unrelated to dose or duration of stimulant therapy. Mean age of subjects was 11 years. A significant correlation occurred between younger age and development of tics. As the authors noted, these children may have developed tics, regardless of [treatment with the medications](#) in question [42].
- c) [Tourette syndrome](#) may be precipitated with the use of stimulant medications in the treatment of [attention deficit disorders](#) in children. Early signs of [Tourette syndrome](#) are difficult to distinguish from the [attention deficit disorder](#) symptoms. Children may therefore be mistakenly treated with additional stimulant medications. Stimulants may exacerbate severe motor and phonic tics; discontinuation of the stimulants and the possible initiation of [haloperidol](#) therapy is often required. In patients diagnosed as having an [attention deficit disorder](#), a clinical evaluation for tics and [Tourette syndrome](#) in children and their families should precede the use of stimulant medication. The use of [dextroamphetamine](#) is contraindicated in children with [Tourette syndrome](#) or tics. In children with no symptoms of [Tourette's syndrome](#) or tics but with a family history, stimulants should be used very cautiously. If tics emerge during [dextroamphetamine](#) therapy, the drug should be discontinued [43].
- d) These authors present several cases of children with [attention deficit disorders](#) who experienced hyperactivity, attention difficulties, and in some cases, motor tic symptoms. The patients were placed on stimulant therapy and experienced exacerbation or development of tics or [Tourette syndrome](#). [Stimulant withdrawal](#) and [haloperidol](#) therapy controlled the motor and phonic symptoms [44].
- e) Researchers reviewed the medication histories of 200 children with [Tourette syndrome](#). Forty-eight patients had received stimulant drugs: 42 [methylphenidate](#), 5 [dextroamphetamine](#), 13 [pemoline](#). Thirty-nine of the 48 (81%) patients received stimulants after the appearance of the tics. Of these, the stimulant drugs increased tics in 8 patients, caused no change in 22, and decreased tics in one patient. Concomitant [haloperidol](#) therapy resulted in no difference in the incidence or frequency of tics in 8 patients. The patients who developed tics with stimulant therapy showed a decrease in the incidence and frequency after discontinuation of the stimulant [45].
- f) Another report describes 2 cases of hyperactive boys who developed motor and phonic tics during [dextroamphetamine](#) therapy. The tics disappeared in both cases after the discontinuation of

dextroamphetamine and the initiation of haloperidol. The authors suggest that neuroleptic-induced tics may be the result of presynaptic dopamine blockade [46].

### 3.3.9.A.13] Tremor

a) Tremor has been reported with dextroamphetamine therapy [28].

## 3.3.10] Ophthalmic Effects

### 3.3.10.A] Dextroamphetamine Sulfate

#### 3.3.10.A.1] Blurred vision

a) Blurring of vision has been reported with stimulant therapy [28].

#### 3.3.10.A.2] Disorder of accommodation

a) Difficulties with accommodation have been reported with stimulant therapy [28].

#### 3.3.10.A.3] Visual disturbance

a) Visual disturbances, including difficulties with accommodation and blurring of vision, have been reported with stimulant therapy [28].

## 3.3.12] Psychiatric Effects

### 3.3.12.A] Dextroamphetamine Sulfate

#### 3.3.12.A.1] Aggressive behavior

a) Aggressive behavior or hostility has been reported in clinical trials and in the postmarketing surveillance of some ADHD medications. Patients should be monitored for aggressive behavior when starting drug therapy for ADHD [28].

#### 3.3.12.A.2] Dysphoric mood

a) Dysphoria has been reported with dextroamphetamine therapy [28].

b) Dextroamphetamine 0.15 mg/kg IV induced a dysphoric reaction, with drowsiness, annoyance, sadness, and anger in 7 postmenopausal women. Young healthy men, who received the same dose, experienced elation of mood and alertness. All of the patients were screened to rule out physical and mental disorders [63].

#### 3.3.12.A.3] Euphoria

a) Euphoria has been reported with dextroamphetamine therapy [28].

#### 3.3.12.A.4] Obsessive-compulsive disorder

a) One author reports 3 cases of obsessive-compulsive behavior as a result of dextroamphetamine therapy. All patients were diagnosed as suffering from attention deficit disorder. The duration of stimulant therapy before the development of symptoms was 2.5 months, 6 months, and 7 years, and the duration of symptoms was 4 to 7 months [64]. A case of amphetamine-induced compulsive disorder was reported that was responsive to pyridoxine (B6) therapy [65].

### 3.3.12.A.5] Psychotic disorder

a) Psychotic episodes have been reported with recommended doses of [dextroamphetamine](#). Use of [amphetamines](#) may exacerbate symptoms of behavior disturbance and thought disorder in psychotic pediatric patients [28].

b) [Amphetamine psychosis](#) can present with visual, tactile, auditory and/or olfactory hallucinations, depression, euphoria, thought disorders, aggressiveness, suspicion, paranoia, increased motor activity, and concentration difficulties. Discontinuation of the drug and treatment with benzodiazepines have been useful in resolving the symptoms [54][55][56][57][58][59]. The administration of [amphetamines](#) to patients with [schizophrenia](#) has resulted in paranoid or catatonic psychotic behavior [60][61]. Healthy persons who ingest [dextroamphetamine](#) in sufficient doses may develop symptoms clinically indistinguishable from [paranoid schizophrenia](#) [62].

c) It was reported that patients whose urine is acidified with [ammonium chloride](#) have a shorter duration of [amphetamine psychosis](#) (approximately 2 days) than patients with [amphetamine psychosis](#) who have alkaline urine (approximately 4.5 days). It was noted that hallucinatory behavior was the first symptom to clear; this occurred within 1 day [57].

### 3.3.12.A.6] Restlessness

a) Restlessness has been reported with [dextroamphetamine](#) therapy [28].

## 3.3.14] Reproductive Effects

### 3.3.14.A] [Dextroamphetamine Sulfate](#)

#### 3.3.14.A.1] [Erectile dysfunction](#)

a) Impotence has been reported with [dextroamphetamine](#) therapy [28].

#### 3.3.14.A.2] [Increased erection of penis](#)

a) General Information

1) Frequent or prolonged erection has occurred with use [66]

#### 3.3.14.A.3] [Increased libido](#)

a) Changes in libido have been reported with [dextroamphetamine](#) therapy [28].

#### 3.3.14.A.4] [Reduced libido](#)

a) Changes in libido have been reported with [dextroamphetamine](#) therapy [28].

## 3.3.16] Other

### 3.3.16.A] [Dextroamphetamine Sulfate](#)

#### 3.3.16.A.1] [Drug dependence](#)

a) Tolerance, extreme psychological dependence, and severe social disability have been reported with [amphetamine](#) use [28]

#### 3.3.16.A.2] [Drug withdrawal](#)

a) Abrupt discontinuation of prolonged high-dose [dextroamphetamine](#) therapy results in extreme fatigue, mental depression, and changes on the [sleep EEG](#) [28].

#### 3.3.16.A.3] [Heart failure](#)

See Drug Consult reference: Drugs That Cause or Exacerbate [Heart Failure](#)

### 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: Unknown

##### 3) Clinical Management

a) [Amphetamines](#) are not recommended for use during pregnancy except possibly in the case of [narcolepsy](#). When used for medical conditions for which the drug is indicated and according to established regimens, [amphetamines](#) are not expected to create a significant risk for fetal anomalies. However, maternal [abuse of amphetamines](#) does increase the potential risk of maternal, fetal, and neonatal morbidity. Although the existing data are controversial, limited evidence suggests an increased incidence of cardiac defects and [cleft palate](#) in neonates born to mothers taking [amphetamines](#) during pregnancy [83].

##### 4) Literature Reports

a) Eleven infants were born with [biliary atresia](#) to mothers who had taken [amphetamines](#) in various doses during the second and third trimesters (time of development of a biliary tree) [79]. In a controlled group of 50 normal infants, it was noted that 3 of 50 mothers had taken [amphetamines](#).

b) A large prospective, observational study of pregnancy and child development was undertaken related to anorectic drugs ([amphetamines](#) and phenmetrazine) prescribed to gravid women during different stages of pregnancy and evaluated for their [teratogenicity](#) [80]. The severe congenital anomaly rate (SCA) per 100 live-born children at age 5 years did not differ from the SCA rate of the group of children whose mothers did not use these drugs. There was, however, an excess of oral clefts in the offspring of mothers who had [amphetamines](#) prescribed in the first 55 days from the last menstrual period. A rough test of efficacy of anorectic drugs was made by comparing mean weight gain in 4-week periods before and after the prescription; it showed only short-term and limited reduction of weight gain.

c) In a further report, clinicians evaluated the outcome of pregnancy in 52 women who had abused [intravenous injections](#) of [methamphetamine](#) throughout pregnancy, with results being compared to a control group of 52 nonabusing women [81]. Body length, body weight and head circumference was decreased significantly in neonates born to mothers abusing [methamphetamine](#)

during pregnancy. However, the frequency of congenital anomalies was not increased significantly compared to the control group.

d)) A statistically significant correlation between aggressive behavior and [amphetamine](#) exposure during fetal life has been reported [82].

## B)) Breastfeeding

### 1)) 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.

### 2)) Clinical Management

a)) [Amphetamines](#) are concentrated in human breast milk. Adverse effects reported in exposed infants include irritability and poor sleeping patterns [85]. The manufacturer of Adderal(R) suggests that breastfeeding women taking [amphetamines](#) be counseled to refrain from nursing (Prod Info Adderal(R), 2003).

### 3)) Literature Reports

a)) One study reported that concentrations of [amphetamine](#) were 3 and 7 times higher in breast milk than plasma on the 10th and 42nd days after delivery, respectively, following administration of [dextroamphetamine](#) 20 mg daily to a nursing mother with [narcolepsy](#) [84]. No untoward effects occurred in the infant. Although only a small fraction of the maternal dose is expected to be transferred to the infant via breast milk, the authors suggest that patients abstain from long-term nursing during [amphetamine](#) treatment.

### 4)) Drug Levels in Breastmilk

#### a)) [Dextroamphetamine](#) Sulfate

##### 1)) Parent Drug

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

1)) One study reported that concentrations of [amphetamine](#) were 3 and 7 times higher in breast milk than plasma on the 10th and 42nd days after delivery, respectively, following administration of [dextroamphetamine](#) 20 mg daily to a nursing mother with [narcolepsy](#). No untoward effects occurred in the infant. Although only a small fraction of the maternal dose is expected to be transferred to the infant via breast milk, the authors suggest that patients abstain from long-term nursing during [amphetamine](#) treatment [84].

### 3.5] Drug Interactions

#### 3.5.1] Drug-Drug Combinations

##### 3.5.1.A] Abiraterone

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#)

##### 3.5.1.B] Acetazolamide

- 1) Interaction Effect: increased exposure to [amphetamine](#)
- 2) Summary: Avoid concomitant use of [amphetamines](#) and gastrointestinal alkalinizing agents, as increased blood levels and potentiated action of [amphetamine](#) may result. The excretion of [amphetamine](#) is pH dependent and an alkaline urine will significantly increase the half-life[70].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of [amphetamines](#) and gastrointestinal alkalinizing agents as increased blood levels and potentiated action of [amphetamine](#) may result. The excretion of [amphetamine](#) is pH dependent and an alkaline urine will significantly increase the half-life[70].
- 7) Probable Mechanism: decreased renal elimination

##### 3.5.1.C] Almotriptan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical



6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.D] Amineptine

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.E] Amitriptyline

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.F] Amitriptylinoxide

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].



- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

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

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

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

- 1) Interaction Effect: increased exposure to [amphetamine](#)
- 2) Summary: Drugs that tend to alkalinize the urine, such as some thiazide diuretics, reduce the renal elimination of [amphetamines](#) by increasing the urinary pH. Because urinary recovery of [amphetamines](#) is highly dependent on pH, coadministration with some thiazides may lead to prolonged [amphetamine](#) exposure. Since concomitant use of urinary alkalizing agent, including some thiazide diuretics, and an [amphetamine](#) may result in increased blood levels and potentiated action of [amphetamine](#), coadministration should be avoided[75].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of urinary alkalizing agents, including some thiazide diuretics, and [amphetamines](#), as increased blood levels and potentiated action of [amphetamine](#) may result[75].
- 7) Probable Mechanism: decreased renal elimination

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

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor

patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.J] [Buprenorphine](#)

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

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

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

2J) Summary: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

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

**3.5.1.L] Buspirone**

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

**3.5.1.M] Carbamazepine**

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

**3.5.1.N] Chlorothiazide**

- 1) Interaction Effect: increased exposure to [amphetamine](#)
- 2) Summary: Drugs that tend to alkalinize the urine, such as some thiazide diuretics, reduce the renal elimination of [amphetamines](#) by increasing the urinary pH. Because urinary recovery of [amphetamines](#) is highly dependent on pH, coadministration with some thiazides may lead to prolonged [amphetamine](#) exposure. Since concomitant use of urinary alkalizing agent, including some thiazide diuretics, and an [amphetamine](#) may result in increased blood levels and potentiated action of [amphetamine](#), coadministration should be avoided[75].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6J) Clinical Management: Avoid concomitant use of urinary alkalizing agents, including some thiazide diuretics, and [amphetamines](#), as increased blood levels and potentiated action of [amphetamine](#) may result[75].

7J) Probable Mechanism: decreased renal elimination

### 3.5.1.OJ [Chlorpheniramine](#)

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

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

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

2J) Summary: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

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

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

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.R] Clomipramine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.S] Cocaine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.T] Cyclobenzaprine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant

use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

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

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

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

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

#### 3.5.1.W] [Diazoxide](#)



- 1) Interaction Effect: increased exposure to [amphetamine](#)
- 2) Summary: Drugs that tend to alkalinize the urine, such as some thiazide diuretics, reduce the renal elimination of [amphetamines](#) by increasing the urinary pH. Because urinary recovery of [amphetamines](#) is highly dependent on pH, coadministration with some thiazides may lead to prolonged [amphetamine](#) exposure. Since concomitant use of urinary alkalizing agent, including some thiazide diuretics, and an [amphetamine](#) may result in increased blood levels and potentiated action of [amphetamine](#), coadministration should be avoided[75].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of urinary alkalizing agents, including some thiazide diuretics, and [amphetamines](#), as increased blood levels and potentiated action of [amphetamine](#) may result[75].
- 7) Probable Mechanism: decreased renal elimination

#### 3.5.1.X] Dibenzepin

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.Y] Dolasetron

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

**3.5.1.Z] Donepezil**

- 1) Interaction Effect: reduced seizure threshold
- 2) Summary: Seizure threshold lowering effects have been associated with [donepezil](#)[67]. 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](#)[67]. 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.AA] Doxepin**

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

**3.5.1.AB] Duloxetine**

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical



6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

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

### 3.5.1.AC] [Eletriptan](#)

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.AD] [Escitalopram](#)

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

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

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.AF] Fluoxetine

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

2J) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

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

### 3.5.1.AG] Fluvoxamine

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

2J) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

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

coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

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

### 3.5.1.AHJ Frovatriptan

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.AIJ Furazolidone

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

2J) Summary: Use of [dextroamphetamine](#) or lisdexamfetamine concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].

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

8J) Literature Reports

aJ) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

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

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

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

- 1) Interaction Effect: increased exposure to [amphetamine](#)
- 2) Summary: Drugs that tend to alkalinize the urine, such as some thiazide diuretics, reduce the renal elimination of [amphetamines](#) by increasing the urinary pH. Because urinary recovery of [amphetamines](#) is highly dependent on pH, coadministration with some thiazides may lead to prolonged [amphetamine](#) exposure. Since concomitant use of urinary alkalizing agent, including some thiazide diuretics, and an [amphetamine](#) may result in increased blood levels and potentiated action of [amphetamine](#), coadministration should be avoided[75].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of urinary alkalizing agents, including some thiazide diuretics, and [amphetamines](#), as increased blood levels and potentiated action of [amphetamine](#) may result[75].
- 7) Probable Mechanism: decreased renal elimination

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

- 1) Interaction Effect: increased exposure to [amphetamine](#)
- 2) Summary: Drugs that tend to alkalinize the urine, such as some thiazide diuretics, reduce the renal elimination of [amphetamines](#) by increasing the urinary pH. Because urinary recovery of [amphetamines](#) is highly dependent on pH, coadministration with some thiazides may lead to prolonged [amphetamine](#) exposure. Since concomitant use of urinary alkalizing agent, including some thiazide diuretics, and an [amphetamine](#) may result in increased blood levels and potentiated action of [amphetamine](#), coadministration should be avoided[75].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of urinary alkalizing agents, including some thiazide diuretics, and [amphetamines](#), as increased blood levels and potentiated action of [amphetamine](#) may result[75].

7) Probable Mechanism: decreased renal elimination

### 3.5.1.AM] Hydroxytryptophan

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.AN] Imipramine

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.AO] Iproniazid

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

2) Summary: Use of [dextroamphetamine](#) or [lisdexamfetamine](#) concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].

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 stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

### 3.5.1.AP] Isocarboxazid

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

2) Summary: Use of [dextroamphetamine](#) or lisdexamfetamine concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].

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 stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

### 3.5.1.AQ] Levomilnacipran

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major



- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

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

- 1) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: Use of [dextroamphetamine](#) or lisdexamfetamine concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].
- 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 stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

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

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.AT] Lofepramine

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.AU] Lorcaserin

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.AV] Melitracen

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

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



use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

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

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

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

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.AY] [Methylene Blue](#)

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

2) Summary: Use of [dextroamphetamine](#) or [lisdexamfetamine](#) concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].

3) Severity: contraindicated

4) Onset: rapid

- 5) Substantiation: probable
- 6) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].
- 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 stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

### 3.5.1.AZ] Milnacipran

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

### 3.5.1.BA] Mirabegron

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor

patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

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

### 3.5.1.BB| [Mirtazapine](#)

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.BC| [Moclobemide](#)

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

2J) Summary: Use of [dextroamphetamine](#) or lisdexamfetamine concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].

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

8J) Literature Reports

aJ) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

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

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

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

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

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

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

**3.5.1.BG| Ondansetron**

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

**3.5.1.BH| Opipramol**

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

**3.5.1.BI| Oxycodone**

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor

patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

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

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

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

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

2J) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

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

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

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor



patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

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

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

2) Summary: Use of [dextroamphetamine](#) or [lisdexamfetamine](#) concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Dextroamphetamine](#) or [lisdexamfetamine](#) use during or within 14 days following the administration of an MAOI is contraindicated[71][72].

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 stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

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

1) Interaction Effect: increased exposure to [amphetamine](#)

2) Summary: Drugs that tend to alkalinize the urine, such as some thiazide diuretics, reduce the renal elimination of [amphetamines](#) by increasing the urinary pH. Because urinary recovery of [amphetamines](#) is highly dependent on pH, coadministration with some thiazides may lead to prolonged [amphetamine](#) exposure. Since concomitant use of urinary alkalizing agent, including some thiazide diuretics, and an [amphetamine](#) may result in increased blood levels and potentiated action of [amphetamine](#), coadministration should be avoided[75].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of urinary alkalizing agents, including some thiazide diuretics, and [amphetamines](#), as increased blood levels and potentiated action of [amphetamine](#) may result[75].

7) Probable Mechanism: decreased renal elimination

### 3.5.1.BO| [Procarbazine](#)

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

2) Summary: Use of [dextroamphetamine](#) or lisdexamfetamine concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].

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 stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

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

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

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



- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#)

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

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#)

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

- 1) Interaction Effect: [hypertensive crisis](#) (headache, [hyperpyrexia](#), [hypertension](#))
- 2) Summary: Use of [dextroamphetamine](#) or [lisdexamfetamine](#) concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable

- 6) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].
- 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 stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

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

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

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

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

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

### 3.5.1.BV] Safinamide

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

2J) Summary: Use of [dextroamphetamine](#) or lisdexamfetamine concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].

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

8J) Literature Reports

aJ) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

### 3.5.1.BW] Selegiline

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

2J) Summary: Use of [dextroamphetamine](#) or lisdexamfetamine concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].

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

8J) Literature Reports

aJ) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a central nervous system stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

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

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

### 3.5.1.BY] [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[69].
- 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.BZ] [Sodium Bicarbonate](#)

- 1) Interaction Effect: increased exposure to [amphetamine](#)
- 2) Summary: Avoid concomitant use of [amphetamines](#) and gastrointestinal alkalizing agents, as increased blood levels and potentiated action of [amphetamine](#) may result. The excretion of [amphetamine](#) is pH dependent and an alkaline urine will significantly increase the half-life[70].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of [amphetamines](#) and gastrointestinal alkalizing agents as increased blood levels and potentiated action of [amphetamine](#) may result. The excretion of [amphetamine](#) is pH dependent and an alkaline urine will significantly increase the half-life[70].

7) Probable Mechanism: decreased renal elimination

### 3.5.1.CA] St John's Wort

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.CB] Sumatriptan

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.CC] Tapentadol

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

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

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#)

### 3.5.1.CE] [Tianeptine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

### 3.5.1.CF] [Tramadol](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant



use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

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

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

2) Summary: Use of [dextroamphetamine](#) or lisdexamfetamine concomitantly or within 14 days following the administration of an MAOI is contraindicated[71][72]. [Amphetamines](#) stimulate the release of [norepinephrine](#), and the use of MAOIs slows down [amphetamine](#) metabolism, thereby increasing release of [norepinephrine](#) and other monoamines from adrenergic nerve endings. This may result in [hypertensive crisis](#), toxic neurological effects, and [malignant hyperpyrexia](#) [74].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Dextroamphetamine](#) or lisdexamfetamine use during or within 14 days following the administration of an MAOI is contraindicated[71][72].

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 stimulant ([pemoline](#) or [dextroamphetamine](#)) with an MAOI was studied. Some of the patients were also taking medications such as tricyclic antidepressants and [lithium](#), in addition to the study medications. 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, 5 to [hypomania](#) and 1 to mania. No patients developed symptoms of [hypertensive crisis](#) during the study [73].

### 3.5.1.CH| [Trazodone](#)

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical



6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.CI] Trichlormethiazide

1) Interaction Effect: increased exposure to [amphetamine](#)

2) Summary: Drugs that tend to alkalinize the urine, such as some thiazide diuretics, reduce the renal elimination of [amphetamines](#) by increasing the urinary pH. Because urinary recovery of [amphetamines](#) is highly dependent on pH, coadministration with some thiazides may lead to prolonged [amphetamine](#) exposure. Since concomitant use of urinary alkalizing agent, including some thiazide diuretics, and an [amphetamine](#) may result in increased blood levels and potentiated action of [amphetamine](#), coadministration should be avoided[75].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of urinary alkalizing agents, including some thiazide diuretics, and [amphetamines](#), as increased blood levels and potentiated action of [amphetamine](#) may result[75].

7) Probable Mechanism: decreased renal elimination

### 3.5.1.CJ] Trimipramine

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.CK] Tryptophan

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

2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.CL] Venlafaxine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.CM] Vilazodone

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].
- 7) Probable Mechanism: additive serotonergic effect

#### 3.5.1.CN] Vortioxetine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor

patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.CO| Xipamide

1J) Interaction Effect: increased exposure to [amphetamine](#)

2J) Summary: Drugs that tend to alkalinize the urine, such as some thiazide diuretics, reduce the renal elimination of [amphetamines](#) by increasing the urinary pH. Because urinary recovery of [amphetamines](#) is highly dependent on pH, coadministration with some thiazides may lead to prolonged [amphetamine](#) exposure. Since concomitant use of urinary alkalizing agent, including some thiazide diuretics, and an [amphetamine](#) may result in increased blood levels and potentiated action of [amphetamine](#), coadministration should be avoided[75].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concomitant use of urinary alkalizing agents, including some thiazide diuretics, and [amphetamines](#), as increased blood levels and potentiated action of [amphetamine](#) may result[75].

7J) Probable Mechanism: decreased renal elimination

### 3.5.1.CP| Ziprasidone

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

2J) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.CQ| Zolmitriptan

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

2)) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[68].

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[76]. 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 [77][78].

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](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

### 4.1] Monitoring Parameters

A)) [Dextroamphetamine](#) Sulfate

1)) Therapeutic

a)) Physical Findings

1)) ADHD

a)) Improvement in symptoms of ADHD is indicative of efficacy.

**b)** Periodically reassess the need for continued dextroamphetamine sulfate treatment by temporarily withdrawing therapy and monitoring for recurrence of behavioral symptoms and their severity [28]

## **2)** Narcolepsy

**a)** Decreased frequency of narcoleptic attacks is indicative of efficacy.

## **2)** Toxic

### **a)** Physical Findings

**1)** 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 [28]

**2)** 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 [31][32] 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 [31]. 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, including dextroamphetamine sulfate, for ADHD [31][32]:

- 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.

- 3J) Screen ADHD patients for bipolar disorder risk factors (ie, detailed psychiatric history, including family history of suicide, bipolar disorder, and depression) prior to treatment [28].
- 4J) Monitor patients with ADHD for new onset or worsening aggressive behavior or hostility at the start of treatment [28].
- 5J) Monitor growth determinations (body weight and height) in pediatric patients during treatment [28].
- 6J) Observe for digital changes (eg, peripheral vasculopathy, including Raynaud's phenomenon) during ADHD treatment and if needed, conduct further evaluation (eg, rheumatology referral) [28].
- 7J) Evaluate for tics and Tourette's syndrome, especially in pediatrics and their families, prior to treatment [28].

#### 4.2J Patient Instructions

##### AJ) Dextroamphetamine (By mouth)

##### Dextroamphetamine

Treats ADHD. Also treats [narcolepsy](#).

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an [allergic reaction](#) to [dextroamphetamine](#), [amphetamine](#), or similar medicines, or if you have [glaucoma](#), an [overactive thyroid](#), or a history of drug abuse.

How to Use This Medicine:

Long Acting Capsule, Liquid, Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

Short-acting tablet: Take your last dose of the day at least 6 hours before bedtime, unless your doctor gives you other instructions.

Extended-release capsule: It is best to take this medicine in the morning. You may have trouble falling asleep at night if you take it in the afternoon or evening.

Swallow the extended-release capsule whole. Do not crush, break, or chew it.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not use this medicine if you are using or have used an MAO inhibitor within the past 14 days.

Some foods and medicines can affect how [dextroamphetamine](#) works. Tell your doctor if you are also using any of the following:

[Acetazolamide](#), [ammonium chloride](#), antacids, [buspirone](#), [chlorpromazine](#), [ethosuximide](#), [fentanyl](#), glutamic acid, [guanethidine](#), [haloperidol](#), [hydrochlorothiazide](#), [lithium](#), [meperidine](#), [methenamine](#), [omeprazole](#), [phenobarbital](#), [phenytoin](#), [propoxyphene](#), [quinidine](#), [reserpine](#), [ritonavir](#), sodium acid phosphate, [sodium bicarbonate](#), St John's wort, [tramadol](#), or tryptophan supplement

Allergy medicine  
Blood pressure medicine  
Medicine to treat depression (including [desipramine](#), [fluoxetine](#), [paroxetine](#), [protriptyline](#))  
Medicine to treat migraine headaches

Fruit juice and [vitamin C](#) can affect how your body absorbs this medicine.

#### Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have [heart](#) or [blood vessel disease](#), heart rhythm problems, [high blood pressure](#), [thyroid problems](#), [Tourette syndrome](#), or a history of [heart attack](#), [stroke](#), or seizures. Tell your doctor if you or anyone in your family has a history of depression, mental health problems, or drug or alcohol abuse.

This medicine may cause the following problems:

Sudden death in people who have [heart defects](#)  
Serious heart or blood vessel problems, including [heart attack](#) and [stroke](#)  
Unusual changes in behavior or mood  
Slow growth in children  
Peripheral vasculopathy (a blood circulation problem)  
[Serotonin syndrome](#) (when used with certain medicines)

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.

This medicine may make you dizzy or cause blurred vision. Do not drive or do anything else that could be dangerous until you know how this medicine affects you.

Tell any doctor or dentist who treats you that you are using this medicine. This medicine may affect certain medical test results.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

#### Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

[Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing  
Anxiety, restlessness, fast heartbeat, fever, sweating, muscle spasms, twitching, nausea, vomiting, diarrhea, seeing or hearing things that are not there  
Blurred vision or vision changes  
Chest pain that may spread, trouble breathing, nausea, unusual sweating, faintness  
Extreme energy or restlessness, confusion, agitation, unusual moods or behaviors  
Fast, pounding, or uneven heartbeat  
Lightheadedness, dizziness, fainting  
Numb, cold, pale, or painful fingers or toes, unexplained [wounds](#) on your fingers or toes  
Seeing, hearing, or feeling things that are not there  
Seizure

If you notice these less serious side effects, talk with your doctor:

Dry mouth, diarrhea, stomach pain  
Loss of appetite, weight loss  
Trouble sleeping

If you notice other side effects that you think are caused by this medicine, tell your doctor.



### 4.3] Place In Therapy

A)) The primary indication for the use of [amphetamines](#) is the clinical condition of [narcolepsy](#) which relies on the central nervous system (CNS) and respiratory stimulant properties of the drugs. In children with hyperkinesia and other abnormal behavioral problems, the [amphetamines](#) appear of value in combination with other remedial measures to reduce observed motor activity from baseline levels [96]. This reduced observed motor activity from baseline values (in hyperactive children given [dextroamphetamine](#)) accompanied by improved behavior and improved attention seems to occur not only in physically inactive tasks (classroom situations) but also physically active tasks (structured sports situations).

### 4.4] Mechanism of Action / Pharmacology

#### A)) [Dextroamphetamine](#) Sulfate

##### 1)) Mechanism of Action

a)) [Amphetamines](#) are noncatecholamine sympathomimetic amines with CNS stimulant activity. There is no evidence to establish a mechanism of [amphetamines](#) for the mental and behavioral effects in children [53][87].

### 4.5] Therapeutic Uses

#### 4.5.1] FDA Uses

##### 4.5.1.A] [Dextroamphetamine](#) Sulfate

##### 4.5.1.A.1] Attention deficit hyperactivity disorder

##### FDA Labeled Indication

##### a)) Overview

FDA Approval: Adult, no; [Pediatric, yes \(immediate-release, age 3 to 16 years ; sustained-release, age 6 to 16 years\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

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

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

##### b)) Summary:

Indicated for the treatment of [attention deficit disorder](#) with hyperactivity (ADHD) as an integral part of a total treatment, typically including psychological, educational and social measures [1][2]

May cause anxiety in susceptible individuals

##### c)) Adult:

1)) Some adult patients with a diagnosis of hyperactivity have also responded well to [dextroamphetamine](#) therapy despite the purported views that the paradoxical response to stimulant medication is exhibited only in prepubertal children [3][4][5]. One report describes

a 20-year-old male with [hyperkinetic syndrome](#) who responded to [dextroamphetamine](#) with a reduction in anxiety and motor activity, increased concentration, depression of mood, drowsiness, reduction in aggression, and disappearance of [paranoid ideation](#) (DeVeagh-Geiss & Joseph, 1980). The patient also showed typical [amphetamine](#) responses of [tachycardia](#), [hypertension](#), anorexia, and tremor.

**d) Pediatric:**

**1)** Investigators examined 29 children (ages 6 to 13 years) who were referred for evaluation of hyperactivity. Each child was treated with [dextroamphetamine](#), levoamphetamine, or placebo in a random, double-blind fashion. Medication was continued for 3 weeks; after a medication-free week, the procedure was repeated for each drug. While off medication, the hyperactive responders to [amphetamine](#) had a higher predominant beta-frequency (EEG) and shorter latencies of selected EP (evoked potential; visual or auditory) waves than did nonresponders. The authors suggest that electrophysiologic parameters may be of practical use in the selection of potential nonresponders. It was observed that no substantial difference was found in the clinical efficacy between d-amphetamine and l-amphetamine as reported by the parents and teachers [6].

**2)** One study found that once an effective dose of [dextroamphetamine](#) sulfate is determined, tolerance to the medication does not develop. Evidence collected from neurophysiologic tests were used to assess tolerance to [dextroamphetamine](#) in 6 hyperactive children over a 6-week treatment period. The lack of tolerance displayed in this study is encouraging from many points of view, but the small population and short length of the study make generalizations difficult [7].

**3)** Others studied the urinary and plasma monoamines and metabolites within the same clinical sample in 31 children with [attention deficit disorder](#) with hyperactivity treated with [dextroamphetamine](#) (up to 1.5 milligrams/kg/day), [methylphenidate](#) (up to 3 milligrams/kg/day), and placebo in an 11-week, double-blind, crossover trial. Both drugs showed striking clinical efficacy. [Dextroamphetamine](#), but not [methylphenidate](#), lowered urinary and plasma 3-methoxy-4-hydroxyphenyl glycol and whole body [norepinephrine](#) turnover. Either drug did not alter the urinary and plasma concentration of homovanillic acid. [Methylphenidate](#) but not [dextroamphetamine](#) increased plasma norepinephrine. Urinary [epinephrine](#) and metanephrine were increased with both drugs [8].

**4)** Ten boys diagnosed as having [attention deficit disorder](#) with hyperactivity and conduct problems were studied in a double-blind, placebo-controlled, crossover trial to determine the aggression lowering effect of [dextroamphetamine](#). Drug dosages ranged from 15 to 30 milligrams/day (0.75 milligram/kilogram) divided over a 2-week period. The authors concluded that [dextroamphetamine](#) reduced aggression in hyperactive boys especially in playroom observation of overt aggressive behavior [9].

**5)** [Dextroamphetamine](#) in doses ranging from 2.5 to 15 milligrams/day has been found to improve symptoms of HYPERKINESIS, HYPERACTIVITY, or MINIMAL BRAIN DYSFUNCTION in certain selected pediatric patients as measured by increase in attention span and reduction of purposeless activity [10][11][12].

**4.5.1.A.2] Narcolepsy**

**FDA Labeled Indication**

**a) Overview**

FDA Approval: Adult, yes; **Pediatric, yes (age 6 years and older)**

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

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

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

**b) Summary:**

[Dextroamphetamine](#) is indicated for the treatment of [narcolepsy](#), and dosage should be individualized for optimal response [1][1]

[Dextroamphetamine](#) is effective in reducing the frequency and duration of narcoleptic attacks (Schindler, 1985)

See Drug Consult reference: [Narcolepsy](#) and [Cataplexy](#) - Drug Therapy

**4.5.2] Non FDA Uses**

**4.5.2.A] [Dextroamphetamine](#) Sulfate**

**4.5.2.A.1] Cocaine dependence**

**a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

**b) Summary:**

[Dextroamphetamine](#) may diminish cocaine responsiveness [13]

**c) Adult:**

**1) [DEXTROAMPHETAMINE](#)** sustained-release (DEX) appears to warrant further study as agonist treatment for cocaine-dependent patients, based on a double-blind, placebo-controlled trial (n=128). At entry, subjects were randomized to 1 of 3 regimens: placebo, DEX 15 milligrams (mg) later raised to 30 mg, or DEX 30 mg later raised to 60 mg. Study drugs were administered twice daily, within 2 hours of awakening and 6 hours later. The first stabilization period was 10 days in length, followed by a 4-week study period. Then doses were doubled and the second stabilization period lasted for 1 week followed by 8-week study period. Participants attended the clinic twice a week for obtaining medication, providing urine samples, and a once-weekly [behavioral therapy](#) session. Study completion/retention rates were 22.9%, 40.4%, and 8.7% for the placebo group, 15/30-mg group, and the 30/60-mg group, respectively (p=0.0012 for the rate differences). Amphetamine-positive urine screens indicated that compliance in the 2 active treatment groups ranged from 81% to 82%. Urine screens were considered positive for cocaine if benzoylecgonine levels were 300 nanograms/liter or higher. Sixteen subjects had no positive urine screens from intake through

study completion; these subjects were removed from the data set. During the last month of the study, the proportion of cocaine urine screens that were positive approximated 80% for the placebo group, 58% to 59% for the 15/30-mg group, and 32% to 33% for the 30/60-mg group. The difference between the placebo and 30/60-mg group almost reached statistical significance during that last month ( $p=0.061$ ). Scores on the [Beck Depression Inventory](#) declined for the 30/60-mg group, increased for the 15/30-mg group, and remained stable for the placebo group. Six subjects dropped out due to side effects of study medication [13].

#### 4.5.2.A.2] Depression

##### a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

##### b) Summary:

[Dextroamphetamine](#) has been used successfully to treat depression, including AIDS patients with low energy and depression (DSM-III-R)

Placebo-controlled studies are lacking

##### c) Adult:

1) [Dextroamphetamine](#) was found to be effective for treatment of post-stroke depression. Researchers retrospectively evaluated 17 patients with post-stroke depression treated with either [DEXTROAMPHETAMINE](#) or [METHYLPHENIDATE](#) during a 5-year period [14]. Eighty-two percent of patients improved on psychostimulants; 47% of patients demonstrated a marked or moderate improvement in depressive symptoms. No significant difference in efficacy existed between the 2 agents. Patients improved quickly within the first 2 days. Only 3 patients discontinued the psychostimulant treatment due to side effects.

2) A positive therapeutic response to [DEXTROAMPHETAMINE](#) therapy in 3 medically-ill and depressed patients is reported [15]. The patients were diagnosed as having a secondary depression that met DSM-III criteria for major affective disorders preceded by, or concurrent with, a medical illness. In a pilot open-label study, [DEXTROAMPHETAMINE](#) was used successfully to improve depression and low energy in 24 AIDS patients [16].

3) Arousal, mood, and anorexic effects improved in a dose-related manner with [DEXTROAMPHETAMINE](#) therapy. Nine healthy male volunteers were evaluated for the effect of [DEXTROAMPHETAMINE](#) on visual analogue scale (VAS) ratings of hunger, arousal, and mood [17]. Subjects were given placebo, [dextroamphetamine](#) 10 milligrams, and [dextroamphetamine](#) 20 milligrams at weekly intervals. Results showed the anorexic effect of the 2 [dextroamphetamine](#) doses were statistically significant. Subjective ratings of arousal and mood increased in a dose-related manner compared to placebo.

4) One study examined the effect of intravenous [DEXTROAMPHETAMINE](#) in 21 depressed patients [18]. Eleven patients were diagnosed as having unipolar disease and 10 as having [bipolar disease](#). All patients received piribedil (a direct-acting dopamine-agonist) in

slowly increasing doses (100 to 240 milligrams/dose) and [dextroamphetamine](#) 20 milligrams. Results showed consistent psychomotor activation and cognitive improvement following [dextroamphetamine](#) administration, although a range of effects on mood (from euphoria to [dysphoria](#)) was noted.

**a) Combination Therapy**

**1)** The combination of monoamine oxidase (MAO) inhibitors (tranylcypromine, isocarboxazid, phenelzine) and stimulants (amphetamine, methylphenidate) has been effective therapy in severe treatment-resistant depression. In addition, the combination of MAO inhibitors and stimulants plus tricyclic antidepressants (amitriptyline, protriptyline, amoxapine, nortriptyline) has also been effective and safe in this type of intractable depression (Sovner, 1990)[19]. Although no serious side-effects were reported, the combination of these agents in an overdose situation could be fatal. With the advent of newer and safer agents such as the serotonin reuptake inhibitors, the combination of MAO Inhibitors, stimulants, and cyclic antidepressants should have a limited role in the treatment of depression.

**4.5.2.A.3] Mania**

**a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

**b) Summary:**

Case reports have suggested that [amphetamines](#) may be of benefit in the treatment of acute mania [20]

**c) Adult:**

**1)** One group of investigators conducted a study to evaluate the effect of [dextroamphetamine](#) on mania with 6 patients. The patients received [dextroamphetamine](#) 15 milligrams every 6 hours (total daily dose, 60 milligrams) for 72 hours [20]. At the time of treatment termination, 5 of the 6 (83%) patients experienced a 50% or greater reduction in their Raskin Severity of Mania scores, but 5 patients did not complete 3 days of therapy: 2 refused participation, 1 was lethargic and nauseated, 1 complained of "skipped" heart beats, and 1 demonstrated lack of improvement of severe manic symptoms. No patient demonstrated a worsening of manic or other psychiatric symptoms with [dextroamphetamine](#).

**4.5.2.A.4] Personality disorder**

**a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

**b) Summary:**

**Dextroamphetamine**, administered to patients with **borderline personality disorder**, may lead to symptoms of **psychosis** [21][22]

**c) Adult:**

**1) Dextroamphetamine** 30 milligrams was administered to 8 **BORDERLINE PERSONALITY DISORDER** patients in a double-blind, placebo-controlled study. The results were compared to the responses of healthy patients under identical conditions. All patients were medication-free for at least 2 weeks. **Dextroamphetamine** led to symptoms of **psychosis** in 50% of the borderline patients, while none of the healthy patients became psychotic during the procedure. Global feelings of well-being were significantly elevated in the borderline group as compared to the healthy group. Borderline patients had a reduced response to growth hormone after **dextroamphetamine** compared to healthy patients, but this was not significant. The authors conclude that **borderline personality disorder** patients respond differently to **dextroamphetamine** than healthy patients [22].

**2) Researchers** studied 16 patients in whom **borderline personality disorder** was suspected to determine if these patients are prone to **psychosis** following ingestion of a dopamine-agonist. In this double-blind study, none of the patients had been receiving neuroleptic drug therapy before admission. Patients were randomly assigned to receive placebo or 30 milligrams **dextroamphetamine** and then crossed over to the opposite regimen. Three patients received only **dextroamphetamine** because they became transiently psychotic during testing and were given a neuroleptic. Results showed that Brief Psychiatric Rating Scale (BPRS) scores significantly increased from baseline after **dextroamphetamine** administration. Activation and thought disturbance were the symptoms that significantly changed. Those patients with **borderline personality disorder** plus **schizotypal personality disorder** had more psychotic symptoms after receiving **amphetamine** than did the patients with **borderline personality disorder** alone (7.6 +/- 2.8 versus 5.4 +/- 1.4, p=0.06). The authors conclude that not only do borderline patients change significantly following **dextroamphetamine** administration, but that the response to **dextroamphetamine** in borderline patients is not heterogeneous as some patients have a worsening of symptoms while others feel better [21].

**4.5.2.A.5] Schizophrenia**

**a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

**b) Summary:**

[Amphetamine](#) improves symptoms in some patients with [schizophrenia](#).

Dopaminergic functions are reduced in the frontal cortex in [schizophrenia](#); the use of a [dopamine](#) agonist like [dextroamphetamine](#) may enhance cortical function in patients with [schizophrenia](#).

However, because [amphetamines](#) are not selective, it would also increase [dopamine](#) release and block reuptake in subcortical dopaminergic systems, possibly exacerbating psychotic symptoms.

**c) Adult:**

**1)** One report briefly describes 2 patients diagnosed with [schizophrenia](#) and nonresponsive to [neuroleptic therapy](#) that maintained clinical improvement in disease after the initiation of [dextroamphetamine](#) 5 to 10 milligrams/day [23].

**2)** One study demonstrated that intravenous [dextroamphetamine](#) (20 milligrams) induced an acute change in [psychosis](#) more frequently than placebo. Of the 45 drug-free SCHIZOPHRENIC PATIENTS studied, 18 patients worsened, 13 improved, and 14 had no change after [dextroamphetamine](#). Placebo produced no change in 14 patients. The 18 patients who worsened after [dextroamphetamine](#) had an increased cerebrospinal fluid concentration for the main metabolite of [norepinephrine](#), 3-methoxy-4-hydroxyphenylglycol, as compared to those patients who showed improvement. The patients who worsened were also significantly more psychotic at baseline than those patients who indicated no change. The sensitivity to [dopamine](#) stimulation in [schizophrenia](#) is state-dependent and not trait-dependent [24].

**3)** Investigators administered [dextroamphetamine](#) 0.25 milligram/kilogram orally to 21 patients with [chronic schizophrenia](#) in a double-blind, placebo-controlled, crossover study. All patients were receiving [haloperidol](#) 0.4 milligram/kilogram day. The results indicated that as a group, the patients were more active and performed psychomotor tests more quickly while receiving [amphetamine](#). Six patients were judged by clinical raters to have improved in terms of affect, cooperation, and engagement with the environment. However, the authors do not advocate [amphetamine](#) as a routine clinical treatment of [schizophrenia](#) [25].

**4.5.2.A.6) Sleep deprivation**

**a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

**b) Summary:**



[Dextroamphetamine](#) enhanced aviator performance during periods of forced wakefulness and sleep deprivation compared with performance on placebo [26]

c) Adult:

1) Oral [dextroamphetamine](#) (DXT) maintained helicopter pilots (n=6; 5 men, 1 woman) in simulator flight performance during 64-hour sleep-deprivation cycles, based on a double-blind, placebo-controlled trial. The greatest difference in the effects of DXT and placebo occurred during the circadian trough periods (from approximately 0300 to 1200) on the second and third days without sleep (sleep deprivation days 1 and 2, respectively). [Dextroamphetamine](#) 10 milligrams or placebo was given at midnight, 0400, and 0800 on sleep deprivation days 1 and 2 during two 64-hour sleep-deprivation cycles, with a 2-day interval between cycles. Performance on the flight simulator was worse on placebo compared with DXT at 0500, 0900, and 1300 on the first deprivation day, and on all flight-simulation times during the second deprivation day (p less than 0.05). [Electroencephalographic monitoring](#) showed higher delta and theta brain activity (normally predominant during sleep) under placebo relative to DXT. When subjects received DXT, self-perceptions of vigor were maintained, while perceptions of fatigue and confusion were reduced. Also, subjects reported feeling more anger on placebo than DXT. Recovery sleep was lighter after DXT, with disturbed REM sleep. No clinically significant side effects were associated with DXT use [26].

#### 4.6] Comparative Efficacy / Evaluation With Other Therapies

##### 4.6.A] [Diethylpropion](#)

###### 4.6.A.1] [Obesity](#)

a) The [amphetamines](#) ([amphetamine](#) sulfate, [dextroamphetamine](#) sulfate, [methamphetamine](#) HCl) are no longer indicated in the treatment of [obesity](#) due to their high incidence of cardiovascular side effects and high abuse potential [112][113]. [Diethylpropion](#) is as effective as [amphetamines](#) in suppressing appetite [114] but produces minimal cardiovascular effects and has so far a low abuse potential.

##### 4.6.B] [Fenfluramine](#)

###### 4.6.B.1] [Attention deficit hyperactivity disorder](#)

a) [Dextroamphetamine](#) was better than [fenfluramine](#) and placebo in reducing motor activity and in improving behavior ratings in 10 boys with DSM-III diagnoses of [attention deficit disorder](#) with hyperactivity during a randomized, double-blind, crossover trial [97].

b) [Dextroamphetamine](#) sulfate (0.5 milligram/kilogram/day, given in 2 divided doses) was reported effective in the treatment of [attention-deficit disorder](#) with hyperactivity (ADD) in a double-blind comparison with placebo and [fenfluramine](#) [98]. [Dextroamphetamine](#) produced immediate and marked improvement in disruptive, overactive behavior. However, [fenfluramine](#) (in doses of 0.6 milligram/kilogram/day initially, increasing to 2 milligrams/kilogram/day) produced no effect on any behavioral measure. Both drugs reportedly decreased levels of urinary [norepinephrine](#), 3-methoxy-4-hydroxyphenylglycol (MHPG) and vanillylmandelic acid; however, [fenfluramine](#) also produced decreases in plasma MHPG, as well as larger decreases in urinary [norepinephrine](#). Urinary [epinephrine](#) levels were increased with [dextroamphetamine](#) but decreased significantly with [fenfluramine](#). Body weight decreased significantly with both agents. The results of this double-blind, crossover study suggest that [fenfluramine](#) has no beneficial effects on hyperactivity or other behaviors in children with ADD who are responsive to [dextroamphetamine](#) therapy. Differences in efficacy were observed despite the structural similarity of

the 2 agents, as well as some common overall effects on catecholamine metabolism and similar effects on body weight.

#### 4.6.B.2] Obesity

a) **Dextroamphetamine** was superior to **fenfluramine** and placebo in terms of weight loss, **behavioral treatment** participation, extent of eating and exercise habit change in 59 overweight female volunteers during a 5-week, randomized, double-blind study [99]. At the 6-month follow-up, there was no significant differences in mean weight between the 3 treatment groups. Also, none of the groups differed significantly from its mean pretreatment weight. Patients in the **fenfluramine** group reported the most gastrointestinal upset, while the **dextroamphetamine** group reported the most central nervous system stimulation.

b) **Fenfluramine** and **dextroamphetamine** were comparable in the treatment of **obesity**. In a study with **fenfluramine** and **dextroamphetamine**, 30 patients were randomly assigned to 1 of 3 groups: **fenfluramine** 20 mg, **dextroamphetamine** 5 mg, or placebo. Patients were instructed to take one capsule orally three times a day at least one hour before meals. The patients who tolerated the drugs were allowed to increase the dosage to 2 capsules three times a day and were given advice on eating habits, but no specific diet was prescribed. **Fenfluramine** was clearly more effective than placebo and as effective as **dextroamphetamine** in producing weight loss. At 7 weeks, **fenfluramine** patients lost 6.6 pounds compared to 6.2 pounds for **dextroamphetamine** patients. The frequency of adverse effects with **fenfluramine** was significantly higher than with **dextroamphetamine** [100].

#### 4.6.C] Mazindol

##### 4.6.C.1] Narcolepsy

a) **Mazindol** and **dextroamphetamine** were comparable for **narcolepsy** therapy. **Mazindol** was retrospectively compared to **dextroamphetamine** for the treatment of **narcolepsy** in 34 patients [102]. Thirty-two patients had previously received oral **dextroamphetamine** 15 to 60 milligrams daily (mean dose 47 milligrams). Oral **mazindol** was given as an initial dose of 2 milligrams twice a day 7 days after **dextroamphetamine** was discontinued. The dose of **mazindol** was adjusted by clinical response. After 1 year of treatment, the daily **mazindol** doses ranged from 3 to 8 milligrams. In addition to **mazindol**, 25 patients received **clomipramine** and 6 received **clonazepam** for **cataplexy**. **Mazindol** produced sustained improvement in **narcolepsy**, reducing day-sleep attacks by 50%. This response was similar to that seen with **dextroamphetamine**, and both treatments were judged equally effective. However, some patients responded to one drug and not the other. **Mazindol** had no effect on **cataplexy** or **sleep paralysis** and adverse effects were significantly lower with **mazindol** compared to **dextroamphetamine**. **Mazindol** produced less euphoria, sweating, and palpitations. Overall, **mazindol** 6 milligrams/day was considered as effective as **dextroamphetamine** 50 milligrams/day in preventing **narcolepsy**.

##### 4.6.C.2] Obesity

a) **Mazindol** is as effective or more effective than **dextroamphetamine** in the treatment of **exogenous obesity** [103][104]. Comparable doses are **mazindol** 1 milligram three times a day and **dextroamphetamine** 5 milligrams three times a day [104]. **Mazindol** is indicated over **dextroamphetamine** and all **amphetamines** for the treatment of **obesity**. In general, no **amphetamine** is indicated for the treatment of **obesity** due to the high probability for dependence and the lack of significant advantages over other anorectics including **mazindol** [105].

b) **Mazindol** is chemically unrelated to **amphetamine** derivatives; however, the anorectic effects are mediated by similar mechanisms (catecholamines and not serotonergic mechanisms) [106]. **Mazindol** has some advantages over **amphetamine** derivatives due to the lack of euphoric effects and dependence potential [107]. **Mazindol** does produce stimulation to the central nervous system, but the incidence is

lower and the reactions are less severe than with [amphetamines](#) [107]. In addition, [mazindol](#) appears to be relatively safe for the treatment of [obesity](#) when [adult-onset diabetes mellitus](#), mild-to-moderate [hypertension](#), and [rheumatoid arthritis](#) are present [108], whereas [amphetamines](#) should not be used in patients with [hypertension](#) or [diabetes](#).

#### 4.6.D] [Methylphenidate](#)

##### 4.6.D.1] [Attention deficit hyperactivity disorder](#)

**a)** SUMMARY: In comparative studies, Adderall(R) (combination [AMPHETAMINE/DEXTROAMPHETAMINE](#)) and [METHYLPHENIDATE](#) showed similar efficacy in the treatment of attention deficit hyperactive disorder in children. [METHYLPHENIDATE](#) requires twice daily dosing compared to Adderall's once daily doses.

**b)** The racemic mixture of L- and D-amphetamine (ADDERALL (R)) was at least as effective as [methylphenidate](#) ([RITALIN](#) (R)) in the treatment for [attention deficit hyperactivity disorder](#) (ADHD), and was more effective at 4 to 5 hours post-administration (beyond [methylphenidate's](#) expected duration of action). In this within-subject, double-blind, placebo-controlled, crossover study, 25 children with ADHD (mean age 9.6 years) were given [methylphenidate](#) 10 milligram (mg), 17.5 mg, Adderall (R) 7.5 mg, 12.5 mg, and placebo twice a day (at 7:45 a.m. and 12:15 p.m.) in a randomized manner every day for 24 days. Teachers and counselors rated their behavior throughout the day and at times beyond [methylphenidate's](#) expected duration of action (noon and 5 p.m.). Parents rated them at the end of the day and in the evening for possible rebound effects. When compared to placebo, Adderall(R) and [methylphenidate](#) significantly improved in-school behaviors (p less than 0.0001 and 0.001, respectively), classroom measures (p less than 0.0001), recess violations (p less than 0.0001), and after-school behaviors (p less than 0.0001). Drug effects were significantly affected by time (p less than 0.01). Adderall(R) consistently resulted in higher effect size (ES) than [methylphenidate](#) and higher doses consistently resulted in higher ES than lower doses. Adderall(R) was also significantly more effective than [methylphenidate](#) at midday and end of day (p less than 0.05). The ES of both drugs dropped at midday and steadily increased in the afternoon, implicating the possibility of reducing the afternoon dose. Side effects were reported more frequently with Adderall(R) but did not preclude the use of both medications. Only 1 patient was eliminated from the study due to exacerbation of his motor tic condition. Further studies are needed to evaluate the possibility of once daily dosing of Adderall(R), and to compare the efficacy of [methylphenidate](#) to D-amphetamine [109].

**c)** Once-daily Adderall(R) (combination [AMPHETAMINE/DEXTROAMPHETAMINE](#)) appeared to be as effective as twice-daily [METHYLPHENIDATE](#) in the treatment of attention deficit hyperactive disorder in children aged 6 to 12 years, according to a double-blind, placebo-controlled, cross-over study (n=21). Also, a mid-afternoon dose of either Adderall or [methylphenidate](#) (MPH) produced better evening behavior than placebo as determined by parental ratings, although either active treatment tended to induce loss of appetite and sleep difficulties. In a randomized manner every day for 24 study-days, children received each day 1 of 7 treatment protocols: (1)MPH 0.3 milligram/kilogram (mg/kg) at 7:30, 11:30, and 15:30; (2)MPH 0.3 mg/kg at 7:30 and 11:30 and MPH 0.15 mg/kg at 15:30; (3)MPH 0.3 mg/kg at 7:30; (4)Adderall 0.3 mg/kg at 7:30 and 15:30; (5)Adderall 0.3 mg/kg at 7:30 and Adderall 0.15 mg/kg at 15:30; (6)Adderall 0.3 mg/kg at 7:30; or (7)placebo. While twice-daily MPH 0.3 mg/kg did not differ significantly from single morning-dose Adderall 0.3 mg/kg, single morning-dose MPH 0.3 mg/kg produced less significant effects than either once-daily Adderall 0.3 mg/kg or twice-daily MPH 0.3 mg/kg. Morning only MPH began to lose its effectiveness approximately 6.5 hours later. Evening behavior was rated better after MPH 0.3 mg/kg than 0.15 mg/kg. With Adderall, no evening differences were seen after mid-afternoon doses of either 0.3 or 0.15 mg/kg. Children showed differential responses to the 2 drugs. Overall, 25% responded more positively to MPH, 37% responded more positively to Adderall, and 38% responded equally well to both medications. For a few of those responding more positively to MPH, one dose of

MPH was sufficient to carry them all day and into the evening. Fifty percent of those responding more positively to Adderall needed only once-daily dosing of the drug [110].

d) In a direct, double-blind, cross-over comparison of adverse effect profiles, both [DEXTROAMPHETAMINE](#) 0.15 milligram/kilogram (mg/kg) twice daily and [METHYLPHENIDATE](#) 0.3 mg/kg twice daily were well-tolerated in 125 children with [attention deficit disorder](#) (mean age 8.7 years). The only adverse effects reported more frequently during drug therapy than at baseline were appetite suppression (both drugs) and insomnia ([dextroamphetamine](#) only). The mean severity of adverse effects was significantly higher in the [dextroamphetamine](#) group. However, only 1.6% of children in each group had to discontinue therapy because of adverse effects [111].

#### 4.6.E] [Modafinil](#)

##### 4.6.E.1] [Attention deficit hyperactivity disorder](#), Adult

a) Both [modafinil](#) and [dextroamphetamine](#) demonstrated efficacy and were well tolerated in the treatment of [attention deficit hyperactivity disorder](#) (ADHD) in adults. During a double-blind, three-phase crossover study, 22 adults (mean age 40.8 years) who met DSM-IV criteria for ADHD were randomized to [modafinil](#), [dextroamphetamine](#), and placebo. The study design included three, 2-week drug treatment phases which were separated by 4-day washout periods. At the beginning of each drug phase, patients received one capsule twice daily containing 50 milligrams (mg) [modafinil](#), 5 mg [dextroamphetamine](#), or lactose. The dose was increased by an additional capsule twice daily every 1 to 2 days as tolerated up to a maximum of 400 mg [modafinil](#), 40 mg [dextroamphetamine](#), or 8 capsules of lactose. The mean optimum doses of [modafinil](#) and [dextroamphetamine](#) were 206.8 mg/day and 21.8 mg/day, respectively. Rating scales and cognitive testing were completed at baseline and on the last day of each drug treatment phase within 3 hours of the last dose. When compared to placebo, [modafinil](#) and [dextroamphetamine](#) were associated with a significant reduction of ADHD symptoms by the DSM-IV ADHD scale (p less than 0.001). Although not statistically significant, less severe ADHD symptoms were associated with [modafinil](#) compared to [dextroamphetamine](#). Cognitive performance as measured by the Controlled Oral Word Association Test (COWAT) reached trend levels of significance for both active treatments compared to placebo (p less than 0.05). Both [modafinil](#) and [dextroamphetamine](#) were well-tolerated with insomnia, irritability, muscle tension, and appetite suppression being the most commonly reported adverse effects [117].

##### 4.6.E.2] Sleep disorder

a) In studies involving healthy young and elderly subjects, oral [modafinil](#) 100 to 200 milligrams (mg) [modafinil](#) at night was associated with less deterioration of normal sleep than with [dextroamphetamine](#) 10 to 20 mg. Specifically, [dextroamphetamine](#) produced greater impairment of sleep maintenance and sleep architecture, and deterioration of subjective sleep quality. The authors suggest the importance of differentiating "vigilance-promoting" qualities of [modafinil](#) from "vigilance-increasing" properties of [amphetamines](#) [118][119]. However, differences between the 2 agents were not always significant in these studies. Total sleep time and sleep efficiency were also reduced significantly by [modafinil](#) compared to baseline, although less so than with [dextroamphetamine](#).

#### 4.6.F] [Pemoline](#)

##### 4.6.F.1] [Attention deficit hyperactivity disorder](#)

a) [Dextroamphetamine](#) and [pemoline](#) are comparable for the treatment of [attention deficit disorder](#). Magnesium [pemoline](#) was compared to [dextroamphetamine](#) in a double-blind, randomized, placebo-controlled study of 81 children with minimal [brain dysfunction](#) [101]. Patients received a maximum dose of 125 milligrams magnesium [pemoline](#) (mean 82 milligrams) and 40 milligrams of [dextroamphetamine](#) (mean

20 milligrams). All psychological tests were administered at baseline and at 8 weeks. At both 4 and 8 weeks, both drugs were superior to placebo. By 8 weeks, 96% of the [dextroamphetamine](#) patients, 77% of the [pemoline](#) patients, and 30% of the placebo patients were improved. The five-factor teacher symptom rating showed significant ( $p$  less than 0.003) changes for defiance, inattentiveness, and hyperactivity factors with both drugs by the end of the study. [Dextroamphetamine](#) showed a significant effect at 2 weeks ( $p=0.057$ ) and at 4 weeks ( $p=0.022$ ) compared to [pemoline](#). Only after 6 weeks did [pemoline](#) show clear differences from placebo. After 8 weeks, however, the 2 treatments were indistinguishable for these factors. Anxiety and sociability were not significantly improved with either drug. On the eight-factor parent symptom list, conduct disturbance, impulsivity, immaturity, and antisocial behavior were significantly improved ( $p$  less than 0.04). Factors not affected were anxiety, somatic complaints, obsessional traits, and hyperactivity. A response was seen with [dextroamphetamine](#) at 2 weeks and no difference between the 2 drugs was demonstrated at 8 weeks. The psychological test battery showed a significant drug improvement over placebo ( $p$  less than 0.004) in spelling, reading, [Porteus Mazes](#), Frostig perceptual quotient, eye-motor coordination, and figure-ground scores. No significant drug-drug differences were noted. The major side effects with both drugs were insomnia and anorexia; insomnia occurred between the 17th and 28th days of therapy. Less than 5% of patients on [dextroamphetamine](#) experienced moderate or severe insomnia by the end of the treatment period. Physiological and psychological heterogeneity exists among children with minimal [brain dysfunction](#). A child should receive drug therapy only after a careful assessment of the probability that he will respond has been determined.

#### 4.6.G] [Phentermine](#)

##### 4.6.G.1] [Obesity](#)

a) Despite differences in the pharmacologic effects and toxicity of the available anorexiant agents, all of the drugs produce the same degree of weight loss and no drug has been found superior to [dextroamphetamine](#) [115]. In addition, the Food and Drug Administration (FDA) Bureau of Drugs has indicated that [amphetamines](#) have no advantages over other anorectic agents that have a lower degree of adverse effects [116]. [Diethylpropion](#), [mazindol](#), and [phentermine](#) are the preferred drugs for the management of [obesity](#), based upon their low degree of euphoriant properties and central nervous system or cardiovascular toxicity [115].

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