Dextroamphetamine-Amphetamine

Sharbaf Shoar N, Marwaha R, Molla M.

Continuing Education Activity

Dextroamphetamine/amphetamine belongs to a class of drugs known as central nervous system stimulants. The Drug Enforcement Administration/Food and Drug Administration classifies these medications as schedule II drugs with high potential for abuse in the United States. Immediate-release and sustained-release amphetamine medications are FDA-approved to treat ADHD and narcolepsy in both adult and pediatric populations. Non-FDA-approved clinical uses for dextroamphetamine/amphetamine include cerebrovascular accidents. This activity will highlight the mechanism of action, adverse event profile, approved and off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, relevant interactions of dextroamphetamine/amphetamine, pertinent for interprofessional team members using these medications for their intended indications.

Objectives:

- Identify the mechanism of action of dextroamphetamine/amphetamine.
- Review the approved and off-label indications for dextroamphetamine/amphetamine.
- Summarize the contraindications and adverse events associated with dextroamphetamine/amphetamine therapy.
- Explain the importance of interprofessional communication in improving care coordination among the interprofessional team when initiating dextroamphetamine/amphetamine therapy.

Access free multiple choice questions on this topic.

Indications

Dextroamphetamine/amphetamine belongs to a class of drugs known as central nervous system stimulants. The Drug Enforcement Administration/Food and Drug Administration (DEA/FDA) classifies these medications as schedule II drugs with high potential for abuse in the United States. Based on the published data by the American Psychiatric Association, 3% to 7% of school-aged children and 4% of adults in the United States have a diagnosis of attention-deficit/hyperactivity disorder (ADHD). Immediate-release amphetamine medication and sustained-release amphetamine medication are used to treat ADHD and narcolepsy in both the adult and pediatric populations.[1][2]

Non-FDA-approved clinical uses for dextroamphetamine/amphetamine:

Cerebrovascular Accident

- FDA approval: Adult, no; Pediatric, no
- Recommendation: Adult, Class III (et al.)
- Strength of evidence: Adult, Category B

Research by Walker-Batson et al. in 1995 and Crisostomo et al. in 1988 shows that amphetamine use in patients with ischemic stroke improved motor function compared with patients undergoing physical therapy alone. However, another study showed conflicting results, as the mean scores on the Fugl-Meyer motor scale were not significant for the amphetamine group compared with the placebo group.

Amphetamine/dextroamphetamine is used off-label by college students for memory enhancement, test-taking ability, and study marathons.

FDA-approved clinical uses for dextroamphetamine/amphetamine:

Attention Deficit Disorder with Hyperactivity

Dextroamphetamine/amphetamine is FDA-approved for adult and pediatric (ages 3 to 16 years) populations. Amphetamines, along with other remedial measures such as psychological, educational, and social, are prescribed to manage patients with symptoms like distractibility, short attention span, hyperactivity, and impulsivity.

In the pediatric population, the immediate-release tablet is recommended for patients three years of age or older, and the extended-release capsule can be prescribed to patients six years or older.

- Adult, Category B Class IIb (Class ll; have a high potential for abuse and dependence, an accepted medical use, and the potential for severe addiction)
- Pediatric, Category B, Class IIb

Narcolepsy

Dextroamphetamine/amphetamine is FDA-approval for adult and pediatric patients who are six years of age or older.

- Adult, Category B, Class IIb
- Pediatric, Category B, Class IIb

Amphetamines are Pregnancy Category C (prior to 2015) (Category C; Animal reproduction studies have shown an adverse effect on the fetus, but no adequate and well-controlled studies in humans. Potential benefits may warrant use in women who are pregnant.)

The American Academy of Pediatrics rates amphetamines as drugs of abuse for which there are reports of adverse effects on the infant during breastfeeding.

Consider potential risks and benefits before prescribing amphetamines during pregnancy and breastfeeding. Use during pregnancy only if the potential maternal benefit outweighs the potential fetal risk.

Reports exist of increased risk of premature delivery and low birth weight in infants born to mothers with amphetamine dependence as amphetamine crosses the placenta. Reported cases show biliary atresia in infants who were exposed to amphetamine in utero during the second and third trimesters.

Amphetamine should not be prescribed to nursing women as it is excreted in human breast milk. Physicians should consider an alternative medication or advise the patient to discontinue breastfeeding. The result of a study on a nursing mother with the diagnosis of narcolepsy who was receiving a daily dose of 20 mg amphetamine was significant for an elevated level of amphetamine in breast milk compared to maternal plasma. Studies showed amphetamines were 3 and 7 times higher in breast milk than maternal plasma on the 10th and 42nd days after delivery, respectively. Measurable amounts of amphetamine were also present in the urine of the infant.

Mechanism of Action

Amphetamines are non-catecholamines, sympathomimetic amines with central nervous system (CNS) stimulant activity. Amphetamines increase dopamine and norepinephrine in the synaptic space by promoting the release of catecholamines from the presynaptic nerve terminals. They also block norepinephrine and dopamine reuptake into the presynaptic neuron by competitive inhibition. Released norepinephrine affecting both alpha-adrenergic receptor sites and beta-adrenergic receptor sites.[3]

Stimulation of beta-adrenergic receptor sites by these medications increases heart rate, stroke volume, and skeletal muscle blood flow.[4][5]

Alpha-adrenergic stimulation causes vasoconstriction and an increase in total peripheral resistance, leading to elevations of both systolic and diastolic blood pressures, a weak bronchodilator, and respiratory stimulant action.

However, the mechanism of amphetamine's mental and behavioral effects in children is not clearly understood.

Both immediate-release tablets and extended-release capsules contain both enantiomer, d-amphetamine, and l-amphetamine salts in the ratio of 3:1. The bioavailable average half-lives are similar for both the sustained-release capsule and immediate-release tablet.

Duration of action

- The immediate-release tablet is 4 to 6 hours; the extended-release is 8 to 12 hours.

Half-life Elimination

- Children 6 to 12 years: D-enantiomer: 9 hours; L-enantiomer: 11 hours
- Adolescents 13 to 17 years: D-enantiomer: 11 hours; L-enantiomer: 13 to 14 hours
- Adults: D-enantiomer: 10 hours; L-enantiomer: 13 hours

Time to Peak

- Immediate release tablet: 3 hours; extended-release: 7 hours

Administration

Dextroamphetamine/amphetamine administration is via the oral route. Prescriptions can be as a tablet (immediate-release) or capsule (extended-release).

Dosage Forms

- Extended-release capsule: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg
- Tablet: 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg

Extended-release capsules should be swallowed whole (without chewing), or the entire capsule may be sprinkled on food and consumed immediately. Do not divide the dose of a single capsule.

Patients should avoid afternoon or late evening doses due to insomnia caused by dextroamphetamine/amphetamine.

The temperature of 20 to 25 degrees C (68 to 77 degrees F) is the preferred temperature to store the medication.

FDA Dosage for Management of Attention Deficit Hyperactivity Disorder

Pediatric

Younger than 3 years

Dextroamphetamine/amphetamine is not recommended for children younger than 3 years of age.

Three to 5 years

An immediate-release tablet is used for children 3 to 5 years of age. Clinicians should evaluate the potential for misuse by the patient or parents before prescribing the short-acting tablets.

- An initial dose of 2.5 mg of an immediate-release tablet once daily in the morning. The first dose should be upon awakening. Subsequent doses of immediate-release tablets may be at intervals of 4 to 6 hours.
- Increase daily dose by 2.5 mg at weekly intervals until reaching the optimal response.
- The dosage range is 2.5 to 40 mg per day, given in 1 to 3 divided doses.

Six years and older

Both immediate-release tablets and extended-release capsules are appropriate for children 6 years of age and older.

Immediate-release tablet:

- An initial dose of 5 mg once or twice daily. The first dose should be upon awakening. Subsequent doses of immediate-release tablets may be at intervals of 4 to 6 hours.
- Increase daily dose by 5 mg weekly until obtaining an optimal response.
- The dosage range is 5 to 40 mg per day in 1 to 3 divided doses.

Extended-release capsule:

- An initial dose of 5 to 10 mg once daily in the morning.
- Increase daily dose by 5 to 10 mg weekly until obtaining an optimal response.
- The maximum daily dose is 30 mg.

Adolescents

Both immediate-release tablets and extended-release capsules are appropriate for this age.

Immediate release:

- An initial dose of 5 mg once or twice daily. The first dose should be upon awakening. Subsequent doses of immediate-release tablets may be at intervals of 4 to 6 hours.
- Increase daily dose by 5 mg weekly until obtaining an optimal response.
- The dosage ranges from 5 to 40 mg per day in 1 to 3 divided doses.

Extended-release capsule:

- An initial dose of 10 mg once daily in the morning.
- Increase to 20 mg daily after one week if needed. There is no adequate evidence that higher doses afford additional benefits.

Adult

Immediate release tablet:

- An initial dose of 5 mg once or twice daily
- Increase daily dose by 5 mg weekly until obtaining an optimal response
- Usually, dosage range from 5 to 40 mg per day in 1 to 3 divided doses. Subsequent doses may be at 4 to 6 hours intervals

Extended-release capsule:

- An initial dose of 20 mg once daily in the morning;
- Based on the available evidence, higher doses (up to 60 mg per day) do not provide additional benefits.

FDA Dosage for management of Narcolepsy

Pediatric (6 years or older)

- An initial dose of 5 mg immediate-release tablet daily.
- Increase daily dose by 5 mg weekly until obtaining an optimal response.
- Usually, the dosage ranges from 5 to 60 mg per day in 1 to 3 divided doses.

Adult

- An initial dose of 10 mg immediate-release tablet once daily in the morning.
- Increase daily dose by 10 mg weekly until obtaining an optimal response.
- Usual dosage range: 5 to 60 mg per day in 1 to 3 divided doses

There are no specific dosage adjustments provided in the manufacturer's labeling for patients with renal or hepatic impairment and geriatric population, but dextroamphetamine/amphetamine should be used with caution and start at the low end of the dosage range.

Adverse Effects

Common

- Cardiovascular: Increased systolic arterial pressure
- Neurologic: Headache, insomnia
- Endocrine metabolic: Weight loss
- Gastrointestinal (GI): Dry mouth, decrease in appetite, weight loss, abdominal pain, nausea, diarrhea
- Psychiatric: Feeling nervous, mood swings

Serious

- Cardiovascular: Cardiomyopathy, myocardial infarction, peripheral vascular disease, Raynaud disease, sudden cardiac death
- Neurologic: Cerebrovascular accident, seizure
- Dermatologic: Stevens-Johnson syndrome, toxic epidermal necrolysis
- Immunologic: Hypersensitivity reaction
- Psychiatric: Psychotic disorder such as new or worsening psychotic or manic symptoms, behavior changes, or emotional lability

Contraindications

- Advanced arteriosclerosis
- Symptomatic cardiovascular disease

- Agitated states
- Concomitant use or use within 14 days of MAOI administration, including linezolid or IV methylene blue, may result in hypertensive crisis.
- Glaucoma
- History of drug abuse
- Hypersensitivity or idiosyncrasy to amphetamine or other product components
- Hyperthyroidism
- Moderate to severe hypertension

Caution is necessary when prescribing stimulants for ADHD to patients with comorbid conditions such as pre-existing psychosis and bipolar illness because they may worsen behavior disturbances and thought disorders that might occur in these patients. Detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression screening, should be considered in these patients to evaluate the risk of bipolar disorder.

Cardiovascular Events (US black box warning)

Sudden death is one of the main concerns associated with CNS stimulant treatment. Misuse or even usual doses of amphetamine in children and adolescents with structural cardiac abnormalities or other serious heart problems may cause sudden death and serious cardiovascular adverse events. Avoid prescribing amphetamine to patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that could increase the risk of sudden death.

Evaluating cardiovascular status in patients before the initiation of stimulant medication is highly recommended. A careful history and physical exam, including all the possible risk factors such as a family history of sudden death or ventricular arrhythmia, should undergo assessment for the presence of cardiac disease. Additional cardiac evaluation with electrocardiogram and echocardiogram should take place if finding suggests cardiac disease.

Abuse/Misuse/Diversion (US black box warning)

Amphetamines are DEA Schedule II controlled substances with a high potential for misuse and dependence. Avoid administration for extended periods as it may lead to drug dependence. Particular attention should focus on the possibility of subjects obtaining amphetamines for non-therapeutic use. The drug should not be distributed to others, and healthcare professionals should prescribe or dispense the medication sparingly.

Assess the risk of abuse before prescribing, and monitor for signs of misuse and dependence while on therapy. Clinicians should exercise caution with this drug in patients with a history of ethanol or drug use disorder.

Documentation strongly suggests the interaction with concurrent use of amphetamine and monoamine oxidase inhibitor drugs is contraindicated as it may result in a hypertensive crisis.

Although available documentation is poor, pharmacologic considerations lead physicians to suspect the interaction of amphetamine and thiazide diuretics. The interaction may be life-threatening as it may result in increased exposure to amphetamine.

Concurrent use of amphetamine and serotonergic agents that inhibit CYP2D6 may increase amphetamine exposure and increase the risk of serotonin syndrome.

Concurrent use of ascorbic acid and amphetamines may cause decreased amphetamine efficacy in patients.[6][7][8]

Monitoring

- Monitor improvement in mental and behavioral symptoms of patients diagnosed with attention-deficit/hyperactivity disorder (ADHD). Reevaluate the patient for the long-term usefulness of the drug by temporarily withdrawing therapy.
- Monitor decreased frequency of narcoleptic attacks.
- Evaluate cardiovascular status before and during treatment. Conduct a further evaluation of any patient who develops any symptoms indicative of a cardiac condition, including exertional chest pain, palpitations, near syncope, or syncope during treatment with stimulants.
- Evaluate ADHD patients for bipolar disorder risk factors before starting the treatment.
- Monitor pediatric patients with new-onset or worsening aggressive behavior after starting the treatment
- Monitor growth in pediatric patients during treatment.

- Evaluate for any sign of peripheral vasculopathy such as Raynaud phenomenon, tics, and Tourette syndrome before and during treatment.

Toxicity

Methamphetamine abuse became an epidemic during the last decade and is one of the main concerns. Increased rates of depression, suicidal ideation, and attempts are seen more in the methamphetamine-abusing adolescent patient population. Twenty to 25 mg/kg is reportedly the lethal dose in the adult population, but the dose-response is variable between the patients. Chronic amphetamine abusers may develop tolerance to up to 15,000 mg/day without lethal results.[9][10][11]

The mechanism of toxicity is primarily related to excessive extracellular dopamine, norepinephrine, and serotonin. The primary clinical syndrome involves prominent neurological and cardiovascular effects, but secondary complications can involve renal, muscle, pulmonary, and GI effects.

Hyperactivity, hyperthermia, tachycardia, tachypnea, mydriasis, tremors, seizures, and altered mental status are some of the most common signs and symptoms of amphetamine intoxication. Diagnosis can be confirmed by detecting amphetamine in stomach contents or vomitus or by positive urine toxicology for illicit drugs. False-positive amphetamine screen can present following trazodone overdose or bupropion overdose.

There is no antidote for amphetamine toxicity; however, activated charcoal is an emergency treatment. In patients who can drink safely, the recommendation to administer activated charcoal, 1 to 2 g/kg up to 100 g by mouth if the ingestion occurred within the previous hour.

Amphetamine-related toxicity requires management by controlling life-threatening central nervous system and cardiovascular signs in a quiet environment. Hospital supportive care includes monitoring the airway, breathing, and circulation. Agitation and seizures are controllable with benzodiazepines, phenothiazines, pentobarbital, and propofol. A beta-blocker such as propranolol can help to manage cardiac tachyarrhythmias. Consider intravenous nitroprusside (start at 0.5 to 1 mcg/kg per minute and titrate as needed) for severe hypertension. Intravenous fluid should be given as it counters hyperthermia, assists in maintaining renal function, and helps promote the elimination of amphetamine and its analogs.

In cases of severe agitation, clinicians should consider aggressive treatment to avoid malignant hypertension, rhabdomyolysis, hyperthermia, and seizures. Evidence supports using large doses of benzodiazepines to treat amphetamine-overdose-related psychosis and agitation. In cases where agitation, delirium, and movement disorders are unresponsive to benzodiazepines, second-line therapies include antipsychotics such as ziprasidone or haloperidol, central alpha-adrenoreceptor agonists such as dexmedetomidine, or propofol can be administered. Neuromuscular paralysis, intubation, and active cooling measures may be necessary in severe cases. In patients with tachycardia, obtain ECG, and consider telemetry. Use intravenous fluid and sedation to control cardiac symptoms. In cases of severe hypertension, consider intravenous nitroprusside. Starting 0.9% normal saline and monitoring creatine kinase (CK), electrolytes, and creatinine is the best way to manage rhabdomyolysis.

There are case reports regarding the Takotsubo cardiomyopathy (TTC), also known as stress-induced cardiomyopathy, which is triggered by amphetamine overdose. In one case, a patient presented to the emergency department after ingesting 30 amphetamine salt tablets with symptoms of chest pain and shortness of breath. At the time of presentation, cardiac enzymes were elevated, the electrocardiogram was unremarkable, and ejection fraction (EF) was 25% to 30% with severe hypokinesis. However, 24 hours later, symptoms were resolved, and a repeated echocardiogram performed three days later showed an EF of 60% with no regional wall motion abnormalities.

Enhancing Healthcare Team Outcomes

All interprofessional healthcare team members should know the potential complications with amphetamine-like agents. This team includes clinicians, specialists, mid-level practitioners, nurses, and pharmacists. These agents should not be prescribed liberally, and even when prescribed, the patient must have close monitoring to ensure that there is no misuse of the medication.

A careful history, physical exam, and cardiovascular evaluation should take place before initiating stimulant medication because serious cardiac problems can increase the risk of sudden death. Evaluate and monitor the risk of abuse and dependence before prescribing amphetamines and during therapy. Physicians should avoid prescribing the immediate-release (short-acting) type if there is a suspicion of potential for misuse in the patient or the parents. The prescribing physician should advise the patient to report symptoms of tachycardia, hypertension, angina, peripheral vasculopathy, or Raynaud

phenomenon. Also, patients should receive education regarding the most common adverse effect of the medication. Most amphetamine-related toxicity is safely manageable with supportive care, including monitoring airway, breathing, and circulation and controlling agitation with benzodiazepines.

With interprofessional care coordination and open communication among the interprofessional team members, patients are more likely to experience therapeutic benefits and avoid adverse events and toxicity when prescribed amphetamine-like agents. [Level 5]

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

References

1. Chen LY, Crum RM, Strain EC, Alexander GC, Kaufmann C, Mojtabai R. Prescriptions, nonmedical use, and emergency department visits involving prescription stimulants. J Clin Psychiatry. 2016 Mar;77(3):e297-304. [PMC free article: PMC5903919] [PubMed: 26890573]
2. Lakhan SE, Kirchgessner A. Prescription stimulants in individuals with and without attention deficit hyperactivity disorder: misuse, cognitive impact, and adverse effects. Brain Behav. 2012 Sep;2(5):661-77. [PMC free article: PMC3489818] [PubMed: 23139911]
3. Denzer C, Denzer F, Lennerz BS, Vollbach H, Lustig RH, Wabitsch M. Treatment of Hypothalamic Obesity with Dextroamphetamine: A Case Series. Obes Facts. 2019;12(1):91-102. [PMC free article: PMC6465734] [PubMed: 30844799]
4. Preuss CV, Kalava A, King KC. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Aug 31, 2021. Prescription of Controlled Substances: Benefits and Risks. [PubMed: 30726003]
5. Gnanavel S. Lisdexamfetamine and Secondary Raynaud's Phenomenon. Prim Care Companion CNS Disord. 2018 Sep 13;20(5) [PubMed: 30256542]
6. Lee NK, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: A systematic review. Drug Alcohol Depend. 2018 Oct 01;191:309-337. [PubMed: 30173086]
7. Castells X, Blanco-Silvente L, Cunill R. Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database Syst Rev. 2018 Aug 09;8:CD007813. [PMC free article: PMC6513464] [PubMed: 30091808]
8. Drugs and Lactation Database (LactMed) [Internet]. National Library of Medicine (US); Bethesda (MD): 2006. Dextroamphetamine. [PubMed: 30000799]
9. Bello NT, Yeomans BL. Safety of pharmacotherapy options for bulimia nervosa and binge eating disorder. Expert Opin Drug Saf. 2018 Jan;17(1):17-23. [PMC free article: PMC6095708] [PubMed: 29053927]
10. Kotagal S. Treatment of narcolepsy and other organic hypersomnias in children. Paediatr Respir Rev. 2018 Jan;25:19-24. [PubMed: 28735675]
11. Weyandt LL, Oster DR, Marraccini ME, Gudmundsdottir BG, Munro BA, Rathkey ES, McCallum A. Prescription stimulant medication misuse: Where are we and where do we go from here? Exp Clin Psychopharmacol. 2016 Oct;24(5):400-414. [PMC free article: PMC5113141] [PubMed: 27690507]

Publication Details

Author Information

Authors

Nazila Sharbaf Shoar[1]; Raman Marwaha[2]; Mohammed Molla[3].

Affiliations

[1] Ross University School of Medicine

[2] Case Western Reserve Un/MetroHealth MC

[3] Kern Medical

Publication History

Last Update: May 2, 2022.

Copyright

Publisher

StatPearls Publishing, Treasure Island (FL)

NLM Citation

Sharbaf Shoar N, Marwaha R, Molla M. Dextroamphetamine-Amphetamine. [Updated 2022 May 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.