AMPHETAMINE(D)

THERAPEUTICS

Brands  •  Dexedrine  
•  Dexedrine Spansules  
•  Dextro Stat  

Generic?  Yes  
Class  •  Stimulant  

Commonly Prescribed For  
(bold for FDA approved)  
•  Attention deficit hyperactivity disorder  
(ADHD)  (ages 3–16)  
•  Narcolepsy  
•  Treatment-resistant depression  

How The Drug Works  
* Increases norepinephrine and especially dopamine actions by blocking their reuptake and facilitating their release  
•  Enhancement of dopamine and norepinephrine actions in certain brain regions may improve attention, concentration, executive function and wakefulness (e.g. dorsolateral prefrontal cortex)  
•  Enhancement of dopamine actions in other brain regions (e.g., basal ganglia) may improve hyperactivity  
•  Enhancement of dopamine and norepinephrine in yet other brain regions (e.g., medial prefrontal cortex, hypothalamus) may improve depression, fatigue, and sleepiness  

How Long Until It Works  
•  Some immediate effects can be seen with first dosing  
•  Can take several weeks to attain maximum therapeutic benefit  

If It Works (for ADHD)  
•  The goal of treatment of ADHD is reduction of symptoms of inattentiveness, motor hyperactivity, and/or impulsiveness that disrupt social, school, and/or occupational functioning  
•  Continue treatment until all symptoms are under control or improvement is stable and then continue treatment indefinitely as long as improvement persists  
•  Reevaluate the need for treatment periodically  
•  Treatment for ADHD begun in childhood may need to be continued into adolescence and adulthood if continued benefit is documented  

If It Doesn’t Work (for ADHD)  
•  Consider adjusting dose or switching to another formulation of d-amphetamine or to another agent  
•  Consider behavioral therapy  
•  Consider the presence of noncompliance and counsel patient and parents  
•  Consider evaluation for another diagnosis or for a comorbid condition (e.g., bipolar disorder, substance abuse, medical illness, etc.)  
* Some ADHD patients and some depressed patients may experience lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require either augmenting with a mood stabilizer or switching to a mood stabilizer  

Best Augmenting Combos for Partial Response or Treatment Resistance  
* Best to attempt other monotherapies prior to augmenting  
•  For the expert, can combine immediate-release formulation with a sustained-release formulation of d-amphetamine for ADHD  
•  For the expert, can combine with modafinil or atomoxetine for ADHD  
•  For the expert, can occasionally combine with atypical antipsychotics in highly treatment-resistant cases of bipolar disorder or ADHD  
•  For the expert, can combine with antidepressants to boost antidepressant efficacy in highly treatment-resistant cases of depression while carefully monitoring patient  

Tests  
•  Blood pressure should be monitored regularly  
•  In children, monitor weight and height
AMPHETAMINE(D) (continued)

SIDE EFFECTS

How Drug Causes Side Effects
- Increases in norepinephrine peripherally can cause autonomic side effects, including tremor, tachycardia, hypertension, and cardiac arrhythmias
- Increases in norepinephrine and dopamine centrally can cause CNS side effects such as insomnia, agitation, psychosis and substance abuse

Notable Side Effects
- Insomnia, headache, exacerbation of tics, nervousness, irritability, overstimulation, tremor, dizziness
- Anorexia, nausea, dry mouth, constipation, diarrhea, weight loss
- Can temporarily slow normal growth in children (controversial)
- Sexual dysfunction long-term (impotence, libido changes) but can also improve sexual dysfunction short-term

Life-Threatening or Dangerous Side Effects
- Psychotic episodes, especially with parenteral abuse
- Seizures
- Palpitations, tachycardia, hypertension
- Rare activation of hypomania, mania, or suicidal ideation (controversial)
- Cardiovascular adverse effects, sudden death in patients with preexisting cardiac structural abnormalities

Weight Gain
- Reported but not expected
- Some patients may experience weight loss

Sedation
- Reported but not expected
- Activation much more common than sedation

What To Do About Side Effects
- Wait
- Adjust dose
- Switch to a long-acting stimulant
- Switch to another agent

• For insomnia, avoid dosing in afternoon/evening

Best Augmenting Agents for Side Effects
- Beta-blockers for peripheral autonomic side effects
- Dose reduction or switching to another agent may be more effective since most side effects cannot be improved with an augmenting agent

DOsing AND USE

Usual Dosage Range
- Narcolepsy: 5–60 mg/day (divided doses for tablet, once-daily morning dose for Spansule capsule)
- ADHD: 5–40 mg/day (divided doses for tablet, once-daily morning dose for Spansule capsule)

Dosage Forms
- Spansule capsule 5 mg, 10 mg, 15 mg
- Tablet 5 mg scored, 10 mg

How to Dose
- Narcolepsy (ages 12 and older): initial 10 mg/day; increase by 10 mg each week; give first dose on waking
- ADHD (ages 6 and older): initial 5–10 mg/day in 1–2 doses; increase by 5 mg each week; give first dose on waking
- Can give once-daily dosing with Spansule capsule or divided dosing with tablet (every 4–6 hours)

Dosing Tips
- Clinical duration of action often differs from pharmacokinetic half-life
- Immediate-release dextroamphetamine has 3–6 hour duration of clinical action
- Sustained-release dextroamphetamine (Dexedrine spansule) has up to 8-hour duration of clinical action
- Tablets contain tartrazine, which may cause allergic reactions, particularly in patients allergic to aspirin
- Dexedrine spansules are controlled-release and should therefore not be chewed but rather should only be swallowed whole
How to Stop
- Taper to avoid withdrawal effects
- Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder and may require follow-up and reinstitution of treatment
- Careful supervision is required during withdrawal from abusive use since severe depression may occur

Pharmacokinetics
- Half-life approximately 10–12 hours

Drug Interactions
- May affect blood pressure and should be used cautiously with agents used to control blood pressure
- Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid, ascorbic acid, fruit juices, etc.) and urinary acidifying agents (ammonium chloride, sodium phosphate, etc.) lower amphetamine plasma levels, so such agents can be useful to administer after an overdose but may also lower therapeutic efficacy of amphetamines
- Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) and urinary alkalinizing agents (acetazolamide, some thiazides) increase amphetamine plasma levels and potentiate amphetamine’s actions
- Desipramine and protryptiline can cause striking and sustained increases in brain concentrations of d-amphetamine and may also add to d-amphetamine’s cardiovascular effects
- Theoretically, other agents with norepinephrine reuptake blocking properties, such as venlafaxine, duloxetine, atomoxetine, milnacipran, and reboxetine, could also add to amphetamine’s CNS and cardiovascular effects
- Amphetamines may counteract the sedative effects of antihistamines
- Haloperidol, chlorpromazine, and lithium may inhibit stimulatory effects of amphetamines
- Theoretically, atypical antipsychotics should also inhibit stimulatory effects of amphetamines
- Theoretically, amphetamines could inhibit the antipsychotic actions of antipsychotics

Overdose
- Rarely fatal; panic, hyperreflexia, rhabdomyolysis, rapid respiration, confusion, coma, hallucination, convulsion, arrhythmia, change in blood pressure, circulatory collapse

Long-Term Use
- Often used long-term for ADHD when ongoing monitoring documents continued efficacy
- Dependence and/or abuse may develop
- Tolerance to therapeutic effects may develop in some patients
- Long-term stimulant use may be associated with growth suppression in children (controversial)
- Periodic monitoring of weight, blood pressure, CBC, platelet counts, and liver function may be prudent

Habit Forming
- High abuse potential, Schedule II drug
- Patients may develop tolerance, psychological dependence
• Theoretically, amphetamines could inhibit the mood-stabilizing actions of atypical antipsychotics in some patients
• Combinations of amphetamines with mood stabilizers (lithium, anticonvulsants, atypical antipsychotics) is generally something for experts only, when monitoring patients closely and when other options fail
• Absorption of amphetamines is delayed by phenobarbital, phenytoin, ethosuximide
• Amphetamines inhibit adrenergic blockers and enhance adrenergic effects of norepinephrine
• Amphetamines may antagonize hypotensive effects of veratrum alkaloids and other antihypertensives
• Amphetamines increase the analgesic effects of meperidine
• Amphetamines contribute to excessive CNS stimulation if used with large doses of propoxyphene
• Amphetamines can raise plasma corticosteroid levels
• MAOIs slow absorption of amphetamines and thus potentiate their actions, which can cause headache, hypertension, and rarely hypertensive crisis and malignant hyperthermia, sometimes with fatal results
• Use with MAOIs, including within 14 days of MAOI use, is not advised, but this can sometimes be considered by experts who monitor depressed patients closely when other treatment options for depression fail

Other Warnings/Precautions
• Use with caution in patients with any degree of hypertension, hyperthyroidism, or history of drug abuse
• Children who are not growing or gaining weight should stop treatment, at least temporarily
• May worsen motor and phonic tics
• May worsen symptoms of thought disorder and behavioral disturbance in psychotic patients
• Stimulants have a high potential for abuse and must be used with caution in anyone with a current or past history of substance abuse or alcoholism or in emotionally unstable patients
• Administration of stimulants for prolonged periods of time should be avoided whenever possible or done only with close monitoring, as it may lead to marked tolerance and drug dependence, including psychological dependence with varying degrees of abnormal behavior
• Particular attention should be paid to the possibility of subjects obtaining stimulants for nontherapeutic use or distribution to others and the drugs should in general be prescribed sparingly with documentation of appropriate use
• Usual dosing has been associated with sudden death in children with structural cardiac abnormalities
• Not an appropriate first-line treatment for depression or for normal fatigue
• May lower the seizure threshold
• Emergence or worsening of activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of a mood stabilizer and/or discontinuation of d-amphetamine

Do Not Use
• If patient has extreme anxiety or agitation
• If patient has motor tics or Tourette’s syndrome or if there is a family history of Tourette’s, unless administered by an expert in cases when the potential benefits for ADHD outweigh the risks of worsening tics
• Should generally not be administered with an MAOI, including within 14 days of MAOI use, except in heroic circumstances and by an expert
• If patient has arteriosclerosis, cardiovascular disease, or severe hypertension
• If patient has glaucoma
• If patient has structural cardiac abnormalities
• If there is a proven allergy to any sympathomimetic agent

SPECIAL POPULATIONS

Renal Impairment
• No dose adjustment necessary

Hepatic Impairment
• Use with caution
Breast Feeding
- Some drug is found in mother’s breast milk
  ✽ Recommended either to discontinue drug or bottle feed
- If infant shows signs of irritability, drug may need to be discontinued

Cardiac Impairment
- Use with caution, particularly in patients with recent myocardial infarction or other conditions that could be negatively affected by increased blood pressure
- Do not use in patients with structural cardiac abnormalities

Elderly
- Some patients may tolerate lower doses better

Children and Adolescents
- Safety and efficacy not established in children under age 3
- Use in young children should be reserved for the expert
- d-amphetamine may worsen symptoms of behavioral disturbance and thought disorder in psychotic children
- d-amphetamine has acute effects on growth hormone; long-term effects are unknown but weight and height should be monitored during long-term treatment
- Narcolepsy: ages 6–12: initial 5 mg/day; increase by 5 mg each week
- ADHD: ages 3–5: initial 2.5 mg/day; increase by 2.5 mg each week
- American Heart Association recommends EKG prior to initiating stimulant treatment in children, although not all experts agree

Pregnancy
- Risk Category C [some animal studies show adverse effects, no controlled studies in humans]
- There is a greater risk of premature birth and low birth weight in infants whose mothers take d-amphetamine during pregnancy
- Infants whose mothers take d-amphetamine during pregnancy may experience withdrawal symptoms
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
  ✽ For ADHD patients, d-amphetamine should generally be discontinued before anticipated pregnancies

ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- May work in ADHD patients unresponsive to other stimulants
- Established long-term efficacy of immediate-release and spansule formulations

Potential Disadvantages
- Patients with current or past substance abuse
- Patients with current or past bipolar disorder or psychosis

Primary Target Symptoms
- Concentration, attention span
- Motor hyperactivity
- Impulsiveness
- Physical and mental fatigue
- Daytime sleepiness
- Depression

Pearls
- ✽ May be useful for treatment of depressive symptoms in medically ill elderly patients
- ✽ May be useful for treatment of post-stroke depression
- ✽ A classical augmentation strategy for treatment-refractory depression
- ✽ Specifically, may be useful for treatment of cognitive dysfunction and fatigue as residual symptoms of major depressive disorder unresponsive to multiple prior treatments
- ✽ May also be useful for the treatment of cognitive impairment, depressive symptoms, and severe fatigue in patients with HIV infection and in cancer patients
- ✽ Can be used to potentiate opioid analgesia and reduce sedation, particularly in end-of-life management
- ✽ Some patients respond to or tolerate d-amphetamin better than methylphenidate and vice versa
• Some patients may benefit from an occasional addition of 5–10 mg of immediate-release d-amphetamine to their daily base of sustained-release Dexedrine spansules
    ✽ Despite warnings, can be a useful adjunct to MAOIs for heroic treatment of highly refractory mood disorders when monitored with vigilance
    ✽ Can reverse sexual dysfunction caused by psychiatric illness and by some drugs such as SSRIs, including decreased libido, erectile dysfunction, delayed ejaculation, and anorgasmia
• Atypical antipsychotics may be useful in treating stimulant or psychotic consequences of overdose
• Taking with food may delay peak actions for 2–3 hours
• Half-life and duration of clinical action tend to be shorter in younger children
• Drug abuse may actually be lower in ADHD adolescents treated with stimulants than in ADHD adolescents who are not treated

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Suggested Reading


