AMPHETAMINE (D,L)

**Therapeutics**

**Brands**
- Adderall
- Adderall XR
- Evekeo
- Adzenys-XR-ODT
- Dyanavel XR

*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: dopamine, norepinephrine reuptake inhibitor and releaser (DN-RIRe)
- Stimulant

**Commonly Prescribed for**
(bold for FDA approved)
- Attention deficit hyperactivity disorder (ADHD) in children ages 3–12 (Adderall, Evekeo)
- Attention deficit hyperactivity disorder (ADHD) in children ages 6–17 (Adderall XR, Evekeo, Dyanavel XR, Adzenys XR-ODT) and in adults (Adderall XR, Evekeo, Adzenys XR-ODT)
- Narcolepsy (Adderall, Evekeo)
- Exogenous obesity (Evekeo)
- 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 (e.g., dorsolateral prefrontal cortex) may improve attention, concentration, executive function, and wakefulness
- 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,l-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**
- Best to attempt other monotherapies prior to augmenting
- For the expert, can combine immediate-release formulation with a sustained-release formulation of d,l-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
• Before treatment, assess for presence of cardiac disease (history, family history, physical exam)
• Blood pressure should be monitored regularly
• In children, monitor weight and height

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

Tests
Before treatment, assess for presence of cardiac disease (history, family history, physical exam)
• Blood pressure should be monitored regularly
• In children, monitor weight and height

DOSING AND USE

Usual Dosage Range
• Narcolepsy: 5–60 mg/day in divided doses
• ADHD: 5–40 mg/day (divided doses for immediate-release tablet, once daily morning dose for extended-release tablet)
• Exogenous obesity: 30 mg/day in divided doses

Dosage Forms
• Immediate-release Adderall tablet 5 mg double-scored, 7.5 mg double-scored, 10 mg double-scored, 12.5 mg double-scored, 15 mg double-scored, 20 mg double-scored, 30 mg double-scored
• Immediate-release Evekeo tablet 5 mg scored, 10 mg double-scored
• Extended-release orally disintegrating tablet (Adzenys XR-ODT) 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, 18.8 mg
• Extended-release tablet (Adderal XR) 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg
• Extended-release oral suspension (Dynavel XR) 2.5 mg/mL
**How to Dose**

- Immediate-release Adderall or Evekeo in ADHD (ages 6 and older): initial 5 mg once or twice per day; can increase by 5 mg each week; maximum dose generally 40 mg/day; split daily dose with first dose on waking and every 4–6 hours thereafter
- Immediate-release Evekeo in ADHD (ages 3 to 5): initial 2.5 mg/day; can increase by 2.5 mg each week; administered in divided doses
- Immediate-release Adderall or Evekeo in narcolepsy (ages 12 and older): initial 10 mg/day; can increase by 10 mg each week; split daily dose with first dose on waking and every 4–6 hours thereafter
- Immediate-release Evekeo in narcolepsy (ages 6 to 12): initial 5 mg/day; can increase by 5 mg each week; administered in divided doses
- Extended-release tablet in ADHD: initial 10 mg/day in the morning; can increase by 5–10 mg/day at weekly intervals; maximum dose generally 30 mg/day
- Immediate-release Evekeo in exogenous obesity (ages 12 and older): usual daily dose 30 mg; taken in divided doses of 5–10 mg, 30–60 minutes before meals

**Dosing Tips**

- Clinical duration of action often differs from pharmacokinetic half-life
  - Immediate-release d,l-amphetamine has 3–6 hour duration of clinical action
  - Extended-release d,l-amphetamine has up to 8-hour duration of clinical action
- Adderall XR is controlled-release and should not be chewed but rather should only be swallowed whole
- Extended-release oral suspension (Dyanavel XR) and extended-release orally disintegrant tablet (Adzenys XR-ODT) should not be substituted for other amphetamine products on a mg-per-mg basis due to differing amphetamine base compositions and pharmacokinetic profiles
- Controlled-release delivery of d,l-amphetamine is sufficiently long in duration to allow elimination of lunchtime dosing
- This innovation can be an important practical element in stimulant utilization, eliminating the hassle and pragmatic difficulties of lunchtime dosing at school, including storage problems, potential diversion, and the need for a medical professional to supervise dosing away from home
- Avoid dosing late in the day because of the risk of insomnia
- May be possible to dose only during the school week for some ADHD patients
- Off-label uses are dosed the same as for ADHD
  - May be able to give drug holidays over the summer in order to reassess therapeutic utility and effects on growth and to allow catch-up from any growth suppression as well as to assess any other side effects and the need to reinstitute stimulant treatment for the next school term
  - Side effects are generally dose-related
  - Taking with food may delay peak actions for 2–3 hours

**Overdose**

- Rarely fatal; panic, hyperreflexia, rhabdomyolysis, rapid respiration, confusion, coma, hallucinations, convulsions, 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

**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
Theoretically, atypical antipsychotics should also inhibit stimulatory effects of amphetamines

Pharmacokinetics

- Adderall and Adderall XR are a mixture of d-amphetamine and l-amphetamine salts in the ratio of 3:1
- A single dose of Adderall XR 20 mg gives drug levels of both d-amphetamine and l-amphetamine comparable to Adderall immediate-release 20 mg administered in 2 divided doses 4 hours apart
- In adults, half-life for d-amphetamine is 10 hours and for l-amphetamine is 13 hours
- For children ages 6–12, half-life for d-amphetamine is 9 hours and for l-amphetamine is 11 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 alkalizing agents (sodium bicarbonate, etc.) and urinary alkalizing 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 amphetamine and may also add to 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

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
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SPECIAL POPULATIONS

Renal Impairment
- No dose adjustment necessary

Hepatic Impairment
- No dose adjustment necessary

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

Pregnancy
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLRR or final rule) applies only to prescription drugs and will be

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

- 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,l-amphetamine

(continued)
phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• Infants whose mothers take d,l-amphetamine during pregnancy may experience withdrawal symptoms
• In rat and rabbit studies, amphetamine D,L did not affect embryofetal development or survival throughout organogenesis at doses of approximately one and a half and eight times the maximum recommended human dose of 30 mg/day (child)
• In animal studies, D-amphetamine caused delayed skeletal ossification and decreased post-weaning weight gain in rats; no major malformations occurred in rat or rabbit studies
• Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus

✽ For ADHD patients, d,l-amphetamine should generally be discontinued before anticipated pregnancies

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

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• May work in ADHD patients unresponsive to other stimulants, including pure d-amphetamine sulfate
• New sustained-release option

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
• 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
• Some patients respond to or tolerate d,l-amphetamine better than methylphenidate and vice versa
• Adderall and Adderall XR are a mixture of d-amphetamine and l-amphetamine salts in the ratio of 3:1
• Specifically, Adderall and Adderall XR combine 1 part dextro-amphetamine saccharate, 1 part dextro-amphetamine sulfate, 1 part d,l-amphetamine aspartate, and 1 part d,l-amphetamine sulfate
This mixture of salts may have a different pharmacologic profile, including mechanism of therapeutic action and duration of action, compared to pure dextro-amphetamine, which is given as the sulfate salt.

Specifically, d-amphetamine may have more profound action on dopamine than norepinephrine whereas l-amphetamine may have a more balanced action on both dopamine and norepinephrine.

Theoretically, this could lead to relatively more noradrenergic actions of the Adderall mixture of amphetamine salts than that of pure dextro-amphetamine sulfate, but this is unproven and of no clear clinical significance.

Nevertheless, some patients may respond to or tolerate Adderall/Adderall XR differently than they do pure dextro-amphetamine sulfate.

Adderall XR capsules also contain 2 types of drug-containing beads designed to give a double-pulsed delivery of amphetamines to prolong their release.

Suggested Reading


