Amphetamine/Dextroamphetamine Mixture

<table>
<thead>
<tr>
<th>Generic names</th>
<th>Amphetamine/dextroamphetamine mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available brands</td>
<td>Adderall, Adderall XR</td>
</tr>
<tr>
<td>Available strengths and formulations</td>
<td>5-mg, 7.5-mg, 10-mg, 12.5-mg, 15-mg, 20-mg, and 30-mg tablets (Adderall)</td>
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<tr>
<td></td>
<td>5-mg, 10-mg, 15-mg, 20-mg, 25-mg, and 30-mg extended-release capsules (Adderall XR)</td>
</tr>
<tr>
<td>Available in generic</td>
<td>Yes</td>
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</tbody>
</table>

**GENERAL INFORMATION**

Adderall (amphetamine/dextroamphetamine mixture) is a psychostimulant, or simply a stimulant. Adderall immediate-release tablets and the extended-release capsules contain a mixture of amphetamine and dextroamphetamine. Amphetamine has two mirror-image forms known as enantiomers: levoamphetamine and dextroamphetamine. The two enantiomers have the exact same chemical composition but differ in their spatial orientation (one cannot be superimposed on the other, just as the right and left hands cannot). Dextroamphetamine is the “right-handed” molecule, whereas levoamphetamine is the “left-handed” molecule. Dextroamphetamine is the purified form of amphetamine and the more active of the two enantiomers. Adderall and Adderall XR contain about 75% dextroamphetamine and 25% levoamphetamine. The strength of each Adderall tablet or Adderall XR capsule is given as the total amount of amphetamine and dextroamphetamine.

Adderall is used primarily in treatment of attention-deficit/hyperactivity disorder (ADHD) and narcolepsy, a condition marked by daytime somnolence, in which the person experiences excessive daytime sleepiness. Narcolepsy is a neurological disorder, a dysfunction of the brain in regulating normal sleep-wake cycles. Stimulants allow the person to function during the day. Adderall and Adderall XR were approved by the U.S. Food and Drug Administration (FDA) for treatment of ADHD in both adults and children age 6 years and older. The FDA approved Adderall, but not Adderall XR, for treating adults and children age 6 years and older with narcolepsy.

The use of a medication for its FDA-approved indications is called its labeled use. In clinical practice, however, practitioners often prescribe medications for unapproved indications (off-label uses) when published clinical studies indicate the efficacy, and the standards of medical practice support the safety, of those treatments. Stimulants are also used outside their approved indications. Adderall, for example, may be used to augment antidepressants in treating depression that fail to respond to standard antidepressant therapy. Stimulants in combination with antidepressants can provide symptomatic relief and improvement beyond that experienced with antidepressants alone.
Numerous clinical studies and years of experience have established the safety and effectiveness of stimulants for children with ADHD. Stimulants increase the child’s ability to concentrate, extend attention span, and decrease hyperactivity, allowing uninterrupted learning during the child’s school years. Adults with ADHD also benefit from treatment with stimulants. Stimulants help them to concentrate and remain focused on tasks, increase their attention span, and decrease impulsivity and hyperactivity.

Using stimulants to treat ADHD seems counterintuitive. How do the stimulants help control the symptoms of ADHD? Current research suggests that the pathophysiology of ADHD is associated with impairment of the neurotransmitter systems in the prefrontal cortex of the brain involving norepinephrine and dopamine. The norepinephrine and dopamine neural pathways in the prefrontal cortex are responsible for modulating many of our cognitive processes known as executive function, including planning, problem solving, and decision making. The distinguishing features of ADHD are inability for sustained attention and lack of inhibitory control. Typically, patients with ADHD manifest the core symptoms of inattention, hyperactivity, and impulsivity. Putatively, stimulants like Adderall, as well as nonstimulants (e.g., atomoxetine), increase these neurotransmitters and improve the balance of norepinephrine and dopamine pathways in the prefrontal cortex, thereby ameliorating symptoms of ADHD to improve cognitive function.

There is reasonable concern that stimulants like amphetamines have a potential for abuse, and chronic recreational use may lead to drug dependence. These concerns are usually associated with patients who have increased their dosage for recreational use many times over what was prescribed, which can lead to psychological dependence. However, under the care of a practitioner, for patients who do not have a history of drug abuse and with close monitoring, there is little risk of misuse and dependence.

Adderall is a closely regulated controlled substance. Prescriptions are carefully monitored, and practitioners must write a new prescription each time with no refills for the pharmacy to dispense the medication.

**Dosing Information**

For treatment of ADHD in children ages 3–5 years, the starting dosage for Adderall, or a generic equivalent, is 2.5 mg daily, increased in increments of 2.5 mg weekly as needed. For children age 6 years and older, the recommended starting dosage is 5 mg once or twice a day. The daily dosage is increased by 5 mg in weekly intervals as needed for clinical response without side effects. Similarly, the starting dosage for adults is 5 mg once or twice a day, increased by 5 mg weekly to achieve the optimal clinical response. The maximum recommended dosage for children and adults should not exceed 40 mg/day, except in rare cases.

With convenience of once-a-day dosing, practitioners are more likely to use the extended-release form of Adderall XR. For ADHD, the starting dosage is 20 mg for adults, 5–10 mg for children ages 6–12 years, and 10 mg for adolescents ages 13–17 years, administered once daily in the morning. The daily dosage may be increased 5–10 mg in weekly intervals until clinical response is achieved with minimum side effects. The maximum recommended dosage with Adderall XR, or the generic equivalent, is 60 mg/day for adults, 40 mg/day for adolescents (ages 13–17 years), and 30 mg/day for children (ages 6–12 years).

For treatment of narcolepsy, the starting dosage for adults is 10 mg daily with Adderall (only the immediate-release tablet is approved for narcolepsy), increased in increments of 10 mg weekly as needed to achieve the optimal response. The recommended maximum dosage should not exceed 60 mg/day. For children ages 6–12 years with narcolepsy, the initial dosage is 5 mg once a day, and the usual dosage is 5–60 mg/day in divided doses three to four times a day. For children over age 12 years and older, the dosing is the same as for adults.

**Common Side Effects**

The most common side effects associated with Adderall include rapid heartbeat, increased blood pressure, palpitations, nervousness, insomnia, dry mouth, constipation, nausea, stomachache, constipation, loss of appetite, and weight loss. Side effects may be minimized by starting with a lower dose and
increasing slowly, particularly with smaller children. Stimulants can cause insomnia. When taking Adderall in divided doses, the patient should avoid taking the last dose too close to bedtime; allow at least 4–6 hours after taking the last dose before sleeping. Patients may have fewer problems with insomnia with Adderall XR, with a once-a-day dose early in the morning. Parents and caregivers should monitor children for side effects, especially when starting and increasing the medication.

**Adverse Reactions and Precautions**

Stimulants have a potential for abuse in susceptible individuals. It is unlikely to arise from routine medical use at therapeutic dosages carefully monitored by the practitioner. People who abuse stimulants take amounts many times over that recommended and develop drug tolerance, physical dependence, and social maladaptation and disabilities. With stimulant abuse over prolonged periods, the person develops intractable insomnia, irritability, personality changes, and, in severe cases, psychosis. Heavy use may cause serious cardiovascular adverse reactions, including heart attacks, arrhythmias, strokes, and even sudden death. Patients with a history of alcohol and substance abuse are not appropriate candidates for stimulant therapy.

Stimulants cause an increase in blood pressure and heart rate. Generally, these increases are modest and inconsequential. Caution is indicated for patients with high blood pressure or heart disease. Patients taking a stimulant should routinely check their blood pressure. They should seek medical attention if they experience prolonged headaches, irregular heartbeat, or chest pain.

Sudden death has been reported in children and adolescents with preexisting structural cardiac abnormalities taking stimulants. The association of sudden death with stimulants, however, is indeterminable because patients with serious heart problems carry an increased risk of sudden death. Stimulants should not be used in children and adolescents if they have a heart condition because stimulants can increase their vulnerability to these cardiovascular adverse effects.

Patients with a history of seizure disorder should be cautious while taking Adderall because it can lower the seizure threshold and increase susceptibility for seizures.

For children and adolescents who are still in their growth period, stimulants can suppress linear growth. Practitioners sometimes interrupt dosing on weekends and holidays when children are not in school to allow for growth to catch up. Practitioners routinely measure the height and weight of children taking stimulants. If the children are not growing or gaining weight as expected, their practitioner may interrupt therapy or seek an alternative treatment with a nonstimulant for ADHD.

Adderall may make tics worse in individuals with a tic disorder (i.e., twitching of a muscle group, especially in the face).

**Risk During Pregnancy and Breast-Feeding**

Stimulants are almost never prescribed to women during pregnancy. The safety of Adderall has not been studied in pregnant women. In women who used amphetamines recreationally during pregnancy, the drug did not appear to cause birth defects. In animal reproductive studies, amphetamines did not show fetal malformations. However, prenatal exposure to amphetamines in laboratory animals was associated with long-term neurochemical and behavioral changes that may later affect learning and memory.

Mothers who are dependent on amphetamines while pregnant are at risk of giving birth to babies with complications, including premature delivery, low birth weight, and symptoms of withdrawal. Amphetamines should not be used during pregnancy unless the potential benefits strongly outweigh the potential risk to the fetus. Women of childbearing age should be cautioned of the potential hazards to the fetus if they become pregnant while taking this drug.

Nursing mothers should not take Adderall because small amounts pass into breast milk and are ingested by the baby. If stopping the drug is not an alternative, breast-feeding should not be started or should be discontinued.
Potential Drug Interactions

Monoamine oxidase inhibitors (MAOIs; e.g., phenelzine, isocarboxazid, tranylcypromine, selegiline) are contraindicated with stimulants. Combining the antidepressant MAOIs with amphetamines can precipitate a dangerous elevation of blood pressure known as hypertensive crisis. Amphetamines should not be started for at least 14 days after stopping an MAOI.

Medications for treatment of obesity (e.g., diethylpropion, phentermine, benzphetamine) should not be combined with any stimulant. The combination may increase the stimulatory effects and increase risk of cardiovascular and central nervous system side effects.

Antacids (e.g., aluminum hydroxide, magnesium hydroxide, sodium bicarbonate [Alka-Seltzer]), can decrease the urinary excretion of amphetamines, increasing drug blood levels and risk of adverse effects. Agents that can acidify urine, such as vitamin C (ascorbic acid) and citric acid, may increase urinary excretion of amphetamines, decreasing drug blood levels and reducing the effectiveness of the stimulant.

Carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide) should be avoided with amphetamines. These agents inhibit the action of the carbonic anhydrase enzyme, which converts carbon dioxide and water to bicarbonate and hydrogen, a reversible reaction, in the body. As a result, these medicines may make the urine more alkaline and decrease excretion of amphetamines, potentially increasing the blood levels and toxicity of amphetamines.

Herbal medicines containing ephedra (e.g., traditional Chinese medicine) should be avoided when taking stimulants. Ephedra may dangerously elevate blood pressure or cause cardiac adverse effects (e.g., palpitations) when combined with methylphenidate.

Overdose

The severity of amphetamine overdose varies widely based on the amount ingested, if other drugs are involved, and idiosyncratic reactions to the drug. Toxic symptoms include agitation, restlessness, tremor, panic, hallucinations, psychosis, and rapid respiration. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Adverse cardiovascular events include arrhythmias, elevated blood pressure, and circulatory collapse. Convulsions and coma are poor prognoses and usually precede a fatal overdose.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency department for observation and treatment. The prescription bottle of medication (and any other medication suspected in the overdose) should be brought along as well because the information on the prescription label can be helpful to the treating practitioner in determining the number of pills ingested.

The American Association of Poison Control Centers (www.aapcc.org) can also be contacted via their helpline at 1-800-222-1222, and they can provide the location of the local poison center.

Treatment Summary

- To avoid insomnia, the last daily dose of Adderall should be taken early in the evening and not close to bedtime. Adderall XR should be taken only once a day in the morning.
- Do not take more Adderall than instructed by your practitioner.
- If you miss a dose, take it as soon as possible. If it is close to the next scheduled dose, skip the missed dose and continue on your regular dosing schedule. Do not take double doses. If you missed your dose of Adderall XR in the morning and it is late in the evening, skip the dose and continue on your regular dosing schedule the next morning.
- Adderall may be taken with or without food.
- Do not chew or crush Adderall tablets or Adderall XR capsules; swallow them whole. Take with a full glass of water to help swallow the medication.
• Do not take Adderall at the same time as fruit juices or vitamin C because this can reduce the absorption of the medicine. Check with your practitioner before taking antacids or other vitamins and supplements with your medicine.

• If Adderall causes pronounced nervousness, restlessness, insomnia, loss of appetite, or weight loss, notify your practitioner.

• In children, long-term use of stimulants can slow growth. Inform your practitioner if the child is not growing or gaining weight.

• Store the medication in its originally labeled, light-resistant container, away from heat and moisture. Heat and moisture may precipitate breakdown of your medication, and the medication may lose its therapeutic effects.

• Keep the medication out of the reach of children.

If you have any questions about your medication, consult your medical practitioner or pharmacist.