

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. 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 AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

DESCRIPTION

ADDERALL XR™ is a once daily extended-release, single-entity amphetamine product. ADDERALL XR™ combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate. The ADDERALL XR™ capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from ADDERALL XR™ compared to the conventional ADDERALL® (immediate-release) tablet formulation.

EACH CAPSULE CONTAINS:	<u>5 mg</u>	<u>10 mg</u>	<u>15 mg</u>	<u>20 mg</u>	<u>25 mg</u>	<u>30 mg</u>
Dextroamphetamine Saccharate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Aspartate Monohydrate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Dextroamphetamine Sulfate USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Sulfate USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Total amphetamine base equivalence	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.6 mg	18.8 mg

Inactive Ingredients and Colors: The inactive ingredients in ADDERALL XR™ capsules include: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, opadry beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5 mg, 10 mg, and 15 mg capsules also contain FD&C Blue #2. The 20 mg, 25 mg, and 30 mg capsules also contain red iron oxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Pharmacokinetics

Pharmacokinetic studies of ADDERALL XR™ have been conducted in healthy adult and pediatric (6-12 yrs) subjects, and pediatric patients with ADHD. Both ADDERALL® (immediate-release) tablets and ADDERALL XR™ capsules contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of ADDERALL® (immediate-release), the peak plasma concentrations occurred in about 3 hours for both d-amphetamine and l-amphetamine.

The time to reach maximum plasma concentration (T_{max}) for ADDERALL XR™ is about 7 hours, which is about 4 hours longer compared to ADDERALL® (immediate-release). This is consistent with the extended-release nature of the product.

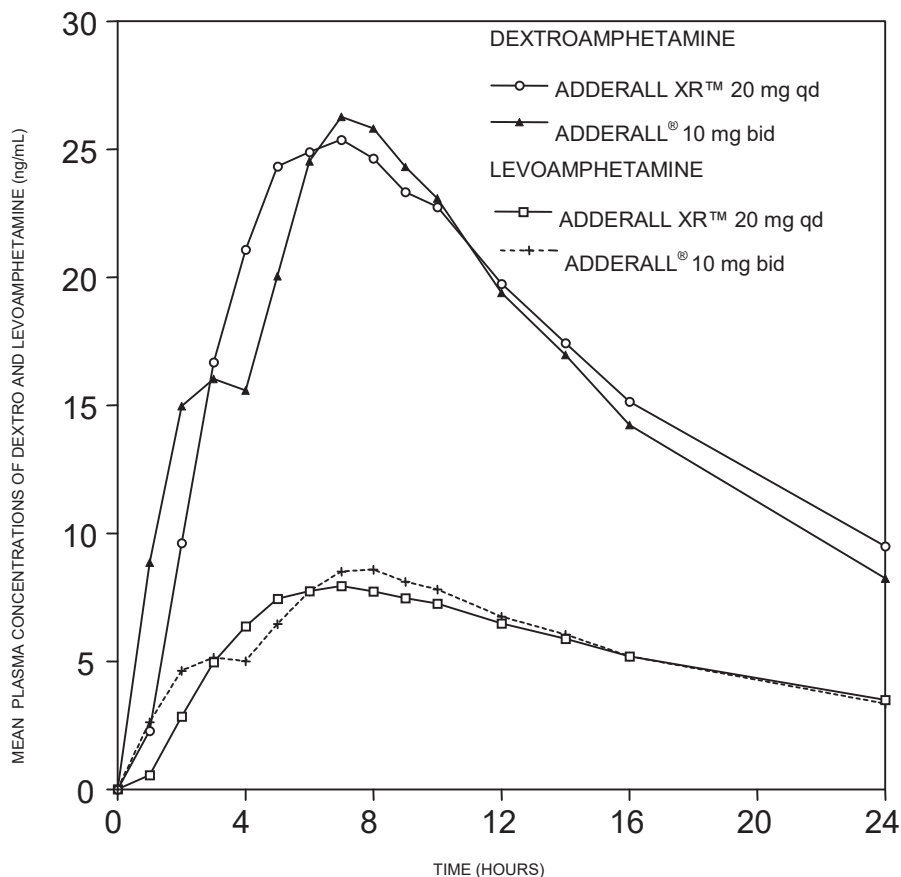


Figure 1 Mean d-amphetamine and l-amphetamine plasma concentrations following administration of ADDERALL XR™ 20 mg (8am) and ADDERALL® (immediate-release) 10 mg bid (8am and 12 noon) in the fed state.

A single dose of ADDERALL XR™ 20 mg capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to ADDERALL® (immediate-release) 10 mg bid administered 4 hours apart.

The mean elimination half-lives for d-amphetamine and l-amphetamine in adults are 10 hours and 13 hours, respectively. In children aged 6 to 12 years, the mean elimination half-life is 1 hour shorter for d-amphetamine (9 hours) and 2 hours shorter for l-amphetamine (11 hours). Children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of ADDERALL XR®, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

ADDERALL XR® demonstrates linear pharmacokinetics over the dose range of 20 to 60 mg in adults and 5 to 30 mg in children aged 6 to 12 years. There is no unexpected accumulation at steady state in children.

Food does not affect the extent of absorption of d-amphetamine and l-amphetamine, but prolongs T_{max} by 2.5 hours (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal for d-amphetamine and 2.1 hours (from 5.6 hrs at fasted state to 7.7 hrs after a high fat meal) for l amphetamine after administration of Adderall XR 30-mg. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state. Equal doses of ADDERALL XR strengths are bioequivalent.

Special Populations

Pediatric Patients

Children eliminated amphetamine faster than adults. The elimination half-life ($t_{1/2}$) is approximately 1 hour shorter for d-amphetamine and 2 hours shorter for l-amphetamine in children than in adults. However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of ADDERALL XR™, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Gender

Systemic exposure to amphetamine was 20-30% higher in women (N=20) than in men (N=20) due to the higher dose administered to women on a mg/kg body weight basis. When the exposure parameters (C_{max} and AUC) were normalized by dose (mg/kg), these differences diminished.

Race

Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=33), Blacks (N=8) and Hispanics (N=10).

Clinical Trials

Children

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in children aged 6-12 (N=584) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to fixed dose treatment groups receiving final doses of 10, 20, or 30 mg of ADDERALL XR™ or placebo once daily in the morning for three weeks. Significant improvements in patient behavior, based upon teacher ratings of attention and hyperactivity, were observed for all ADDERALL XR™ doses compared to patients who received placebo, for all three weeks, including the first week of treatment, when all ADDERALL XR™ subjects were receiving a dose of 10 mg/day. Patients who received ADDERALL XR™ showed behavioral improvements in both morning and afternoon assessments compared to patients on placebo.

In a classroom analogue study, patients (N=51) receiving fixed doses of 10 mg, 20 mg or 30 mg ADDERALL XR™ demonstrated statistically significant improvements in teacher-rated behavior and performance measures, compared to patients treated with placebo.

Adults

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in adults (N=255) who met DSM-IV-TR criteria for ADHD. Patients were randomized to fixed dose treatment groups receiving final doses of 20, 40, or 60 mg of ADDERALL XR® or placebo once daily in the morning for four weeks. Significant improvements, measured with the Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS), an 18-item scale that measures the core symptoms of ADHD symptoms, were observed at endpoint for all ADDERALL XR® doses compared to patients who received placebo for all four weeks. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

INDICATIONS

ADDERALL XR™ is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of ADDERALL XR™ in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12 and one controlled trial in adults who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY), along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance.

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have

persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations: Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program: ADDERALL XR™ is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Long-Term Use: The effectiveness of ADDERALL XR™ for long-term use, i.e., for more than 3 weeks in children and 4-weeks in adults, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ADDERALL XR™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Psychosis: Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

Long-Term Suppression of Growth: Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR generally should not be used in children or adults with structural cardiac abnormalities.

PRECAUTIONS

General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to

minimize the possibility of overdosage.

Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR™, especially patients with hypertension.

Tics: Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Drug Interactions: *Acidifying agents* -Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) lower absorption of amphetamines.

Urinary acidifying agents -These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

Adrenergic blockers -Adrenergic blockers are inhibited by amphetamines.

Alkalinizing agents -Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Co-administration of ADDERALL XR™ and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

Antidepressants, tricyclic -Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO inhibitors -MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines -Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives -Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine -Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide -Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol -Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.

Lithium carbonate -The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meperidine -Amphetamines potentiate the analgesic effect of meperidine.

Methamphetamine therapy -Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methamphetamine therapy.

Norepinephrine -Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital -Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin -Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene -In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum alkaloids -Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

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