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Amphetamine Orally Disintegrating Tablets: Another Option for the Treatment of Attention Deficit Hyperactivity Disorder

Marcia L. Buck, PharmD, FCCP, FPPAG, BCPPS

The options for treatment of attention deficit hyperactivity disorder (ADHD) continue to expand (Table 1). With the approval of Adzenys XR-ODT™ on January 26, 2016, Neos Therapeutics introduced the first extended-release orally disintegrating amphetamine tablet.[1] The manufacturer also has an extended-release methylphenidate ODT in phase 3 clinical trials. The ODT form offers a convenient means of providing 10-12 hours of symptom control for patients unable to swallow tablets or capsules.

Mechanism of Action

While the exact mechanism of central nervous system (CNS) stimulants in the treatment of ADHD has not been established, it is likely related to blocking of norepinephrine and dopamine reuptake at presynaptic neurons and a resulting increase in monoamines within the CNS. Amphetamine XR-ODT contains a 3:1 ratio of d-amphetamine to l-amphetamine. The drug is attached to a mixture of 50% immediate-release and 50% delayed-release polymer-coated resin particles. The resulting product provides 10-12 hours of symptom control.[1]

Pharmacokinetics

The approval of amphetamine XR-ODT was based, in large part, on studies demonstrating equivalent serum concentrations of d- and l-amphetamine to those produced by Adderall XR®. The manufacturer enrolled 42 adults into an open-label randomized crossover study comparing 18.8 mg amphetamine XR ODT, in either a fasting state or after a meal, to 30 mg (the equivalent dose) of Adderall XR®. Thirty-nine subjects completed the trial. The geometric mean ratios of the products for both d- and l-amphetamine were within 80-125%.[2]

Following a single 18.8 mg amphetamine XR-ODT dose in 40 adults, the mean d-amphetamine peak plasma concentration of 44.9 $\pm$ 8.9 ng/mL occurred at a mean time of 5 hours after dosing. The mean l-amphetamine peak of 14.5 $\pm$ 3 ng/mL occurred at 5.25 hours. Administration of a high-fat meal 30 minutes prior to taking a dose resulted in a 19% decrease in the maximum concentration of the d-isomer and a longer time to reach peak concentrations, however neither of these changes was considered clinically significant. Approximately 30-40% of an amphetamine dose is excreted in the urine as unchanged drug. The percentage varies based on urinary pH. The remainder undergoes hepatic metabolism via CYP2D6 oxidation and other pathways. The mean elimination half-life of d-amphetamine is 11.25 $\pm$ 2 hours in adults. Renal or hepatic dysfunction may result in prolonged elimination of amphetamine.[1]

Warnings and Precautions

CNS stimulants, including amphetamine products, should not be used in patients with cardiac disease or in patients with a family history of arrhythmias or sudden cardiac death. Although rare, the risk for sudden cardiac death is higher in pediatric patients with structural cardiac anomalies. Amphetamine use may cause an increase in heart rate or blood pressure. In clinical trials, the mean increases observed with amphetamine administration in adults have been 3-6 bpm and 2-4 mm Hg, respectively. Stimulant use is also associated with peripheral vasculopathy and suppression of growth. The use of CNS stimulants may induce or exacerbate symptoms of pre-existing psychiatric illness or induce a manic episode in patients with bipolar disease.

All CNS stimulants have a high potential for abuse. The risk for abuse should be evaluated prior to initiation of amphetamine products and periodically during treatment.[1] The ODT formulation may be more easily abused than other stimulant dosage forms; patients and families should understand the need for appropriate safeguards surrounding storage and handling of the tablets. Unused tablets should be returned to an appropriate drug take-back program, or if unavailable, mixed with an undesirable non-toxic liquid and placed in a sealed plastic bag prior to being discarded.

Adverse Effects

Based on the results of the bioequivalency study described earlier, the Food and Drug Administration allowed the manufacturer to extrapolate safety data from earlier studies of Adderall XR®. In patients 6 to 12 years of age, the most commonly reported adverse effects in trials of Adderall XR® were loss of appetite, insomnia, abdominal pain, emotional lability, nausea and vomiting, nervousness, and fever. In patients 13 to 17 years of age, the most common reactions were loss of appetite, abdominal pain, weight loss, insomnia, and nervousness.[1]

Drug Interactions

Central nervous system stimulants should not be administered during treatment with or within 14 days of administration of monoamine oxidase (MAO) inhibitors, including selegiline, isocarboxazid, phenelzine, and tranylcypromine. MAO inhibitors slow amphetamine metabolism and may result in increased amphetamine-induced release of norepinephrine from adrenergic nerve endings. This change in catecholamine concentrations can produce a potentially fatal hypertensive crisis, with toxic neurologic effects and malignant hyperpyrexia.[1]

Concomitant administration of tricyclic antidepressants with amphetamines can cause significant increases in d-amphetamine concentrations in the brain and potential amphetamine-related cardiovascular adverse effects. Drugs that alter urinary pH can affect the excretion of amphetamines. Acidifying agents such as ascorbic acid, guanethidine, reserpine, or glutamic acid may decrease blood amphetamine levels and reduce symptom control. Sodium bicarbonate, acetazolamide, or other alkalinizing agents may increase blood amphetamine levels. Administration of amphetamines with proton pump inhibitors may produce a more rapid peak amphetamine concentration and an altered clinical response.[1]

Availability and Cost

Adzenys XR-ODT™ is available in 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg tablets, equivalent to the six strengths of Adderall XR®. The 30-tablet carton is sold with a rigid plastic travel case to protect doses from being crushed after removal from the carton. Additional travel cases are available from the manufacturer by calling 1-888-236-6816.[1] The retail cost for a 30-day supply ranges from approximately $270 to $300, making it comparable to several of the other new once-daily ADHD treatment options.

Dosing

The recommended starting dose for amphetamine XR-ODT is 6.3 mg once daily in the morning. The dose may be increased at weekly intervals by increments of 3.1 or 6.3 mg. The maximum recommended dose is 18.8 mg. The tablets should be removed from the blister pack immediately prior to use with dry hands. The foil should be peeled back to avoid breakage. The tablet should be placed on the tongue and allowed to dissolve in the saliva. The prescribing information contains a chart of equivalent doses for patients transitioning from Adderall XR®.[1]

Summary

With the growing number of options for the treatment of ADHD, prescribers can tailor therapy to the specific needs of the patient. Oral disintegrating tablets offer an alternative to oral solutions for once-daily treatment in patients unable to take a tablet or capsule.

References

1. Adzenys XR-ODT prescribing information. Neo Therapeutics, Inc. January 2016. Available at: http://www.neostxcontent.com/Labeling/Adzenys/Adzenys_PI.pdf (accessed 9/24/16).
2. Stark JG, Engelking D, McMahen R, et al. A randomized crossover study to assess the pharmacokinetics of a novel amphetamine extended-release orally disintegrating tablet in healthy adults. Postgrad Med 2016;128:648-55.

Table 1. Medication Options for the Management of ADHD

Product (Manufacturer)	Formulation	Approximate Duration of Effect	Available Strengths	Dosing Considerations
Methylphenidate				
Ritalin® or generic (Novartis and others)	Immediate-release tablets*	3-4 hours	5, 10, 20 mg	Provides flexibility for initial dose titration
Methylin™ Chewable or generic (Shionogi Pharma and others)	Chewable tablet*	3-4 hours	2.5, 5, 10 mg	Contains phenylalanine
Methylin™ Liquid or generic (Shionogi Pharma and others)	Oral solution	3-4 hours	5 mg/5 mL and 10 mg/5 mL	Grape-flavored solution; store at room temperature
Metadate ER® or generic (UCB, Inc. and others)	Extended-release tablet*	6-8 hours	10, 20 mg	Swallow whole; do not break, crush, or chew
Methylin ER™ (Shionogi Pharma)	Extended-release tablet*	6-8 hours	10, 20 mg	Swallow whole; do not break, crush, or chew
Metadate CD® (UCB, Inc.)	Diffucaps capsule with 30% immediate-release beads and 70% delayed-release beads*	8-10 hours	10, 20, 30, 40, 50, 60 mg	Capsule may be opened and beads swallowed whole with applesauce
Ritalin LA® (Novartis)	Capsule with Spheroidal Oral Drug Absorption System (SODAS) technology; 50% immediate-release beads and 50% delayed-release (2nd peak 4 hrs later)*	8-10 hours	10, 20, 30, 40, 60 mg	Capsule may be opened and beads swallowed whole with applesauce Do not give with antacids or acid suppressants
Aptensio XR™ (Rhodes Pharmaceutical)	Capsule with multilayer beads; 40% of dose in the immediate release layer and 60% in the extended-release layer (2nd peak at 7-8 hrs)	12 hours	10, 15, 20, 30, 40, 50, 60 mg	Capsule may be opened and beads swallowed whole with applesauce
Concerta® or generic (McNeil Pediatrics and others)	Tablet with OROS osmotic pump technology; biphasic release with initial peak at 1 hr (20% of dose) and gradual release over 9 hrs	12 hours	18, 27, 36, 54 mg	Must be swallowed whole; non-absorbable shell may be passed in stool
Daytrana® (Noven Therapeutics)	Transdermal patch with drug dispersed in adhesive layer; applied daily	12 hours with 9 hour wear time	10, 15, 20, 30 mg	The time worn can be varied to control the duration of action; monitor for skin sensitization. Discard patches appropriately
Quillivant XR™ (Pfizer)	Extended-release oral suspension; 20% of the dose is immediate-release and 80% extended-release	12-13 hours	25 mg/5 mL	Fruit-flavored; may be taken with or without food. Shake bottle for at least 10 seconds before preparing the dose. May be stored at room temperature

Dexmethylphenidate				
Focalin® or generic (Novartis and others)	Immediate-release tablets*	4-6 hours	2.5, 5, 10 mg	Active isomer; give approx. ½ methylphenidate dose
Focalin XR® or generic (Novartis and others)	Capsule with SODAS technology; 50% of the beads contained in the capsule are immediate-release and 50% are delayed-release*	12 hours	5, 10, 15, 20, 25, 30, 35, 40 mg	Capsule may be opened and beads swallowed whole with applesauce Do not give with antacids or acid suppressants
Amphetamine				
Adzenys XR-ODT™ (Neo Therapeutics)	Extended-release orally disintegrating tablets: 50% immediate-release and 50% delayed-release particles	10-12 hours	3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg	Allow tablet to dissolve in saliva; do not crush or chew
Dyanavel XR (Tris)	Extended-release oral solution	13 hours	2.5 mg/mL	Bubblegum flavor; may be taken with or without food. Shake bottle before preparing the dose. May be stored at room temperature.
Dextroamphetamine				
Dextroamphetamine (various manufacturers)	Immediate-release tablets or capsules	3-6 hours	2.5, 5, 7.5, 10, 15, 20, 30 mg	Provides flexibility during initial titration
ProCentra® and generic (Independence Pharmaceuticals and others)	Oral solution	3-6 hours	5 mg/5 mL	Colorless, bubble-gum flavor. Store at room temperature
Mixed Amphetamine Salts				
Adderall® or generic (Teva and others)	Immediate-release tablet	4-6 hours	5, 7.5, 10, 12.5, 15, 20, 30 mg	
Adderall® XR or generic (Teva and others)	Capsule with Micotrol delivery system: 50% immediate-release and 50% delayed-release beads*	10-12 hours	5, 10, 15, 20, 25, 30 mg	Capsule may be opened and beads swallowed whole with applesauce
Racemic Amphetamine Sulfate				
Evekeo (Arbor)	Extended-release tablets	10 hours	5, 10 mg	Also FDA approved for the treatment of narcolepsy and short-term treatment of obesity
Lisdexamfetamine				
Vyvanse® (Shire)	Capsule containing lisdexamfetamine (dextroamphetamine linked to l-lysine); peaks in 3.5 hrs*	10-13 hours	10, 20, 30, 40, 50, 60, 70 mg	Capsule may be opened and contents dissolved in water, yogurt, or orange juice; use immediately after dissolving

Atomoxetine				
Strattera® (Lilly)	Capsule*	24 hours	10, 18, 25, 40, 60, 80, 100 mg	Selective norepinephrine inhibitor; may take several weeks to achieve full effect Swallow capsule whole; powder is irritating
Clonidine				
Catapres® or generic (Boehringer Ingelheim and others)	Immediate-release tablets	3-6 hours (wide interpatient variability)	0.1, 0.2, 0.3 mg	Sedating, typically initiated at bedtime; increase weekly by adding morning and then mid-day doses; can be made into an extemporaneous oral liquid formulation
Catapres-TTS® or generic (Boehringer Ingelheim and others)	Transdermal patch, applied weekly	5-7 days	0.1, 0.2, 0.3 mg/24 hours	Potential for skin irritation; if patch loosens, cover with adhesive overlay. Cutting patches to provide a lower dose is not recommended. Discard patches appropriately
Kapvay® (Concordia Pharmaceuticals)	Extended-release tablets	12 hours	0.1, 0.2 mg	Swallow tablet whole; typically dosed twice daily
Guanfacine				
Tenex® or generic (Promius Pharma and others)	Immediate-release tablets	6-12 hours	1, 2 mg	
Intuniv™ or generic (Shire and others)	Extended-release tablet	12-24 hours	1, 2, 3, 4 mg	Swallow tablet whole; a high-fat meal may increase absorption and lead to toxicity

* Administration with a high-fat meal may delay the time to peak serum concentrations, but has no significant effect on total absorption.

All information listed was obtained from product prescribing information and is subject to change. Please contact the manufacturer's website for additional information.

Buck ML. Pediatric Pharmacotherapy October 2016;22(10):1-5.