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Amphetamines in the Treatment of Attention-Deficit/Hyperactivity Disorder **Marcia L. Buck, Pharm.D., FCCP**

This is the second in a series of articles in *Pediatric Pharmacotherapy* focusing on new pharmacologic approaches to the treatment of attention-deficit/hyperactivity disorder (ADHD).^a This issue will describe the use of the amphetamine products in ADHD, the second most frequently prescribed agents for this disorder, and highlight the new extended release product which offers the convenience of once-daily dosing,

Mechanism of Action

Like methylphenidate, the mechanism of action for amphetamines in patients with ADHD is not known. Amphetamines are sympathomimetic agents that cause the release and block the reuptake of norepinephrine and dopamine from central neurons. Their efficacy in ADHD appears to be mediated through increases in these neurotransmitters.^{1,2}

Available preparations

There are currently four different amphetamine preparations on the market in the United States, racemic amphetamine sulfate, dexamphetamine (also referred to as dextroamphetamine or *d*-amphetamine sulfate), methamphetamine (also referred to as desoxyephedrine), and a newer amphetamine mixture. This product, originally marketed as Adderall[®] and now available as a generic, contains equal amounts of four different amphetamine salts: *d*-amphetamine saccharate, *d,l*-amphetamine aspartate monohydrate, *d*-amphetamine sulfate, and *d,l*-amphetamine sulfate. Both isomers of amphetamine are pharmacologically active, but differ in their elimination characteristics.²

Clinical Use

Both methylphenidate and amphetamines have been widely used in the treatment of ADHD for many years. With the availability of newer products and a response rate to methylphenidate of approximately 70%, there appears to be a growing role for amphetamines in the ADHD

population as initial therapy or as second-line agents in children who fail to respond to methylphenidate. Despite the frequent use of these two stimulants, there have been fewer than a dozen comparative trials published in the medical literature and none that demonstrated clear superiority of one drug over the other.³ In the last several years, there has been a renewed interest in comparing ADHD treatments in order to establish a first-line choice and identify patient characteristics that might aid in the selection of the ideal stimulant for an individual child.

In 1997, Efron, Jarman and Baker reported the results of their double-blind crossover trial comparing dexamphetamine (0.15 mg/kg given twice daily) with methylphenidate (0.3 mg/kg given twice daily).³ Immediate release (IR) products were used for both drugs, with doses given after breakfast and lunch. The patients were evaluated at baseline and after a two week trial of each drug using the Conners' Parent Rating Scale-Revised (CPRS-R), the Conners' Teacher Rating Scale-Revised (CTRS-R), the Parental Global Perceptions Questionnaire, and the Continuous Performance Test (CPT). A total of 125 children with ADHD between the ages of 5 to 15 years were enrolled. Mean CPRS-R and CTRS-R scores for both drugs showed considerable improvement compared to placebo over all domains. Although there was a trend toward a greater improvement with methylphenidate, the results were not statistically significant. Likewise, neither parental response on the questionnaires or CPT scores revealed a difference between treatments. The authors were unable to identify any patient characteristics (ie, gender, age, socioeconomic status, or co-morbid states) that correlated with improved response to one particular drug. There was a slightly greater number of adverse effects during the dexamphetamine trial. Based on their observations, the authors concluded that neither drug was clearly superior, but dexamphetamine may have an advantage based on cost.

Two years later, Pelham and colleagues published their double-blind, placebo-controlled crossover comparison of twice daily IR methylphenidate (10 mg or 17.5 mg) and Adderall® (7.5 mg or 12.5 mg).⁴ Drugs and dosages were alternated in a random order with placebo on a daily basis. Twenty-five children (5-12 years of age) were studied in a summer treatment program at the State University of New York at Buffalo. Daily ratings from teachers, parents, and counselors were evaluated, as well as scores on standardized tests. Both drugs were superior to placebo on all testing methods. Adderall® proved to be superior to Ritalin®, particularly when comparing the lower doses (10 mg Ritalin® twice daily versus 7.5 mg Adderall® twice daily. Time-course analysis for both drugs revealed that the afternoon dose appeared to produce a greater effect than the morning dose, prompting the authors to suggest that a lower afternoon dose be administered compared to the morning dose, in patients being treated with immediate release products. .

Later that year, these investigators published the results of another time-course analysis comparing once and twice-daily Adderall® to once, twice, and three-times-daily methylphenidate.⁵ Twenty-one children, ages 5 to 12 years, participated in this placebo-controlled crossover study. As in the previous study, daily crossovers were made to alternate therapies and placebo, with multiple daily assessments. In this study, the single morning dose of Adderall® produced an equivalent effect to the twice-daily methylphenidate. For assessments made in the evening hours, the three-times-daily methylphenidate proved to be superior, but the single daily Adderall® dose still provided a greater improvement in assessment scores over placebo. It should be noted that this study and the one prior to it were supported by a grant from Shire Laboratories, the maker of Adderall®.

While these newer studies, like the earlier papers, have not conclusively identified a drug of choice for children with ADHD, they demonstrate the efficacy and relative safety of both methylphenidate and amphetamines. These studies may have been hampered by the complexity of assessing response to therapy and, in the case of the latter two studies, their small sample size. It appears that either agent may be considered for initiation of treatment, with the option of the alternative agent for those children who fail to respond.

Pharmacokinetics

Amphetamines are slowly, but completely absorbed after oral administration. They are

widely distributed, with high concentrations (5 to 10 mcg/dl) occurring in the brain. Amphetamines are hepatically metabolized by N-dealkylation, oxidative deamination, and to a lesser degree aromatic hydroxylation through the cytochrome P450 enzyme CYP2D6. At normal urinary pH, approximately 30% of an oral dose is excreted unchanged. Urinary excretion of the drug is pH dependent; alkalization of the urine extends the normal 7 to 8 hour half-life to a range of 18 to 35 hours.^{2,6}

Sustained and Extended Release Products

The 3:1 ratio of *d*- to *l*-amphetamine salts in Adderall® was designed to provide a sustained drug effect. While the prolonged effect of this preparation appeared to offer an advantage over IR methylphenidate in the Pelham studies, these trials did not answer the question of whether other amphetamine products could produce a similar effect.

In the November 2001 issue of the *Journal of the American Academy of Child and Adolescent Psychiatry*, James and colleagues published a comparison of the efficacy and time-course of IR and sustained release dexamphetamine (Dexedrine Spansules®) and Adderall®.⁷ Thirty-five children between the ages of 5 and 12 years were enrolled in this double-blind, placebo-controlled crossover study. As anticipated, all treatments were significantly better than placebo at improving behavior ratings, activity measurements, and academic scores. The sustained release dexamphetamine proved to have the least beneficial effect in the early morning assessments, but lasted 3 to 6 hours longer than the other products. Although parental assessments were similar for all treatments up to 12 hours after a single dose, only the sustained release dexamphetamine treatment had a prolonged effect in improving math problem solving ability. The authors suggested that, like other IR products, Adderall® may require twice daily dosing to achieve adequate serum concentrations into the latter part of the day. They propose that sustained release dexamphetamine may provide a better alternative for children requiring a prolonged duration of effect, but may produce inadequate early morning control.

More questions will likely arise with the release of an amphetamine product with an even longer duration of effect. On October 11, 2001, the Food and Drug Administration approved Adderall XR®, an extended release preparation designed to provide once daily dosing that would last until early evening.⁸ The capsule contains both immediate and extended release beads of

the same amphetamine mixture contained in Adderall® tablets. While peak plasma concentrations occur approximately 3 hours after an oral dose of immediate release Adderall®, serum concentrations peak at 7 hours with the extended release product. A single dose of Adderall XR® is considered by the manufacturer to be equivalent to a 10 mg IR dose of Adderall® given twice daily. There are currently no studies in the medical literature comparing this new product to other amphetamine preparations or methylphenidate.

Drug Interactions

The efficacy of beta-adrenergic blocking agents will be counteracted by amphetamines. In addition, amphetamines may decrease the antihypertensive effects of guanethidine. In patients requiring antihypertensives, alternative therapies for ADHD should be considered. Monoamine oxidase inhibitors (MAOIs) and furazolidone, an antimicrobial with MAOI activity, may increase the effects of amphetamines, resulting in significant hypertension. These agents should not be used concurrently, and patients previously receiving MAOIs or furazolidone should wait for at least two weeks before starting therapy with an amphetamine product.

Some patients taking tricyclic antidepressants with amphetamines may experience a change in the efficacy or adverse effects of their antidepressant. Dose adjustment may be necessary in these patients. Amphetamine interactions with the selective serotonin reuptake inhibitors (SSRIs) have not been reported in clinical studies, but the inhibition of CYP2D6 by the SSRIs may have the potential to prolong the elimination of amphetamine products. Amphetamines may delay the gastrointestinal absorption of some anticonvulsants, including phenobarbital, phenytoin, and ethosuximide.

Because drug elimination is dependent on pH, drugs which alter urine pH will affect the serum concentrations of amphetamines. Urinary acidifiers, such as ascorbic acid, will shorten the duration of action of amphetamines, while urinary alkalinizing agents, such as acetazolamide, will prolong the duration of action and may increase the risk for toxicity.^{2,8}

Adverse Effects

The most commonly reported adverse effects with amphetamines are loss of appetite (occurring in approximately 20-25% of patients), insomnia (17-20%), abdominal pain (10-14%), emotional lability (9%), nervousness (6%), and nausea or vomiting (5-7%). Tachycardia,

diarrhea or constipation, dry mouth, fatigue, dizziness, dyskinesia, hypersensitivity reactions, and psychotic symptoms have also been reported with amphetamine use. As with other stimulants, amphetamines may worsen hypertension, exacerbate tic disorders, and unmask or worsen depression.^{2,8-10}

Like methylphenidate, amphetamines have the potential to cause tolerance and psychiatric dependence. All of the amphetamine products are schedule II controlled substances.

Products and Dosing

The following amphetamine products are available for the treatment of ADHD:

- **racemic amphetamine sulfate** (generic)
5 and 10 mg IR tablets
- **dextroamphetamine** (Dexedrine® and generic)
5 and 10 mg IR tablets
5, 10, and 15 mg sustained release tablets
- **methamphetamine** (Desoxyn®)
5 mg IR tablets
5, 10, and 15 mg sustained release tablets
- **amphetamine mixture** (Adderall® or generic and Adderall XR®)
5, 10, 20, and 30 mg IR tablets
10, 20, and 30 mg extended release capsules

In children 6 years of age and older, dosing with IR amphetamine products should be initiated at 5 mg once daily, given in the morning, and increased in increments of 5 mg on a weekly basis until the desired response is obtained. The usual daily dose is in the range of 0.1 to 0.5 mg/kg. In some children, a second or third dose of the IR products may be needed at 4 to 6 hour intervals. Total daily doses above 40 mg are not recommended. In children less than 6 years of age, dosing should begin at 2.5 mg once daily and be increased in 2.5 mg increments each week as needed.²

As with methylphenidate, there are currently no oral liquid dosage formulations of amphetamines on the market for children unable to swallow tablets. The manufacturer of Adderall® has recently published stability data on an extemporaneous oral suspension made with Ora-Sweet®, Ora-Plus®, or a mixture of the two compounding vehicles.¹¹ The resulting suspensions are stable for 30 days at room temperature, providing an alternative for children requiring a liquid dosage form.

Adderall XR® should be initiated at a dose of 10 mg once daily, given in the morning. It may be increased in 10 mg increments each week up to a maximum recommended dose of 30 mg/day. For

children unable to swallow the capsule, the capsule may be opened and the beads sprinkled onto applesauce. The beads should be swallowed whole and not chewed.⁸

Cost

As with methylphenidate, there is a wide range in the cost of amphetamine products. The cost for the newer once-daily stimulants is comparable.

<i>Product and regimen</i>	<i>Cost for 30 days^a</i>
dexamphetamine 5 mg TID (generic)	\$ 24.55
Dexedrine [®] 5 mg TID	33.03
Dexedrine Spansules [®] 10 mg BID	65.58
Adderall [®] 10 mg BID	85.20
Amphetamine mixture 10 mg BID (generic)	72.81
Adderall XR [®] 20 mg QD	70.20

^aBased on average whole sale prices (AWP)

Summary

Amphetamine products, particularly the extended release dosage form, are becoming an increasingly popular choice for the treatment of children with ADHD and a useful alternative in those who fail to respond to methylphenidate. While initial comparisons between the two agents have been limited, these drugs appear to be similar in efficacy. Adverse effects seem milder with methylphenidate, but further evaluation of the newer amphetamine dosage formulations may alter that impression.

^aThese reviews have been developed for a workshop on therapies for behavioral illnesses in children to be given at the 22nd Annual University of Virginia McLemore Birdsong Pediatric Conference from May 17th through 19th. For more information, please contact Shirley P. Newman, Conference Coordinator at 434-924-2554.

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Pharmacology Literature Review

Doxapram associated with QT prolongation

Because of its adverse effect profile, doxapram is typically reserved for those patients with apnea of prematurity who fail therapy with methylxanthines. In this prospective study of 40 infants receiving doxapram (0.5-1 mg/kg/hr IV), a statistically significant, but moderate, increase in the QT interval was found. Six patients had a clinically significant prolongation (greater than 440 ms) but no rhythm disturbances. The authors suggest that infants placed on doxapram should be monitored for this potentially serious adverse effect. Maillard C, Boutroy M, Fresson J, et al. QT interval lengthening in premature infants treated with doxapram. *Clin Pharmacol Ther* 2001;70:540-5.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 2/22/02:

1. Intracavernosal alprostadil (Caverject[®]) was added for the evaluation of erectile dysfunction.
2. Extended release methylphenidate (Concerta[®]) was added to the Formulary. For more information on this product, refer to the February 2002 issue of *Pediatric Pharmacotherapy*. Ritalin SR[®] was deleted.
3. Budesonide (Entocort EC[®]) was added for the management of Crohn's disease.
4. Paricalcitol (Zemlar[®]) was added for patients with renal failure requiring dialysis who are unable to tolerate or are resistant to calcitriol.

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