

Triple-bead mixed amphetamine salt for ADHD

Jeffrey R. Strawn, MD, and Lara S. Picard, PharmD

Stimulants are first-line psychopharmacologic interventions for attention-deficit/hyperactivity disorder (ADHD), and their efficacy is supported by clinical trials and meta-analyses in children and adolescents¹ as well as adults.² Despite decades of tolerability and efficacy data supporting their use, a major drawback of stimulants is that their salutary therapeutic effects wane once the medication is cleared or metabolized. Both mixed amphetamine- and methylphenidate-based preparations have short half-lives, necessitating multiple doses per day (eg, 3 or 4 times a day) when short-acting preparations are used. Over the past 15 years, nearly a dozen formulations were developed that extend the duration of action through delayed release, delayed absorption, or utilizing prodrugs.

In June 2017, long-acting, triple-bead mixed amphetamine salt (MAS) was FDA-approved under the brand name Mydayis for the once-daily treatment of ADHD in adolescents (age ≥ 13) and adults (*Table 1*).³ This formulation utilizes a unique triple-bead technology to extend its duration of action. When this technology was developed—nearly a decade ago—it was hoped that the duration of action of the stimulant would be significantly increased, beyond the 10- to 12-hour duration of action of available stimulants at that time. This newly approved formulation provides 16 hours of coverage, and patients may experience an onset of action within 2 to 4 hours following administration.³

The encapsulated preparation contains 3 MAS beads: an immediate-release amphetamine salt bead, a pulsed-delayed

Table 1 Fast facts about long-acting, triple-bead mixed amphetamine salt

Brand name: Mydayis
Indication: ADHD in patients age ≥ 13 years
Approval date: June 20, 2017
Availability date: Summer 2017
Manufacturer: Shire
Dosing form: 12.5-mg, 25-mg, 37.5-mg, 50-mg extended-release capsules
Recommended dosage: Initiate 12.5 mg, titrated 12.5 mg weekly, to 25 mg/d (adolescents age ≥ 13) or 50 mg/d (adults)
Source: Reference 3

release bead, and an extended-release bead (*Figure 1, page 34*), which give rise to a unique pharmacokinetic profile (*Figure 2, page 35*).³

Mechanism of action

Like all MAS, this formulation blocks the reuptake of norepinephrine and dopamine, increasing synaptic concentrations of these

Dr. Strawn is Associate Professor of Psychiatry, University of Cincinnati, College of Medicine, Cincinnati, Ohio, and Child and Adolescent Section Editor of *CURRENT PSYCHIATRY*. Dr. Picard is Clinical Pharmacist, Mercy Health Partners, Cincinnati, Ohio, and Adjunct Assistant Professor of Pharmacy Practice, University of Cincinnati, James L. Winkle College of Pharmacy, Cincinnati, Ohio.

Disclosures

Dr. Strawn has received research support from Eli Lilly, Edgemont, Shire, Forest Research Laboratories, Lundbeck, the National Institute of Mental Health, and Neuronetics; has received royalties from Springer for the publication of 2 texts; and has received material support from Assurex Health. Dr. Strawn's work with Shire involved guanfacine, extended-release, for anxiety disorders in youth. He has not been involved in any advisory role, clinical trials, or promotional speaking for the compound featured in this article. Dr. Picard reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

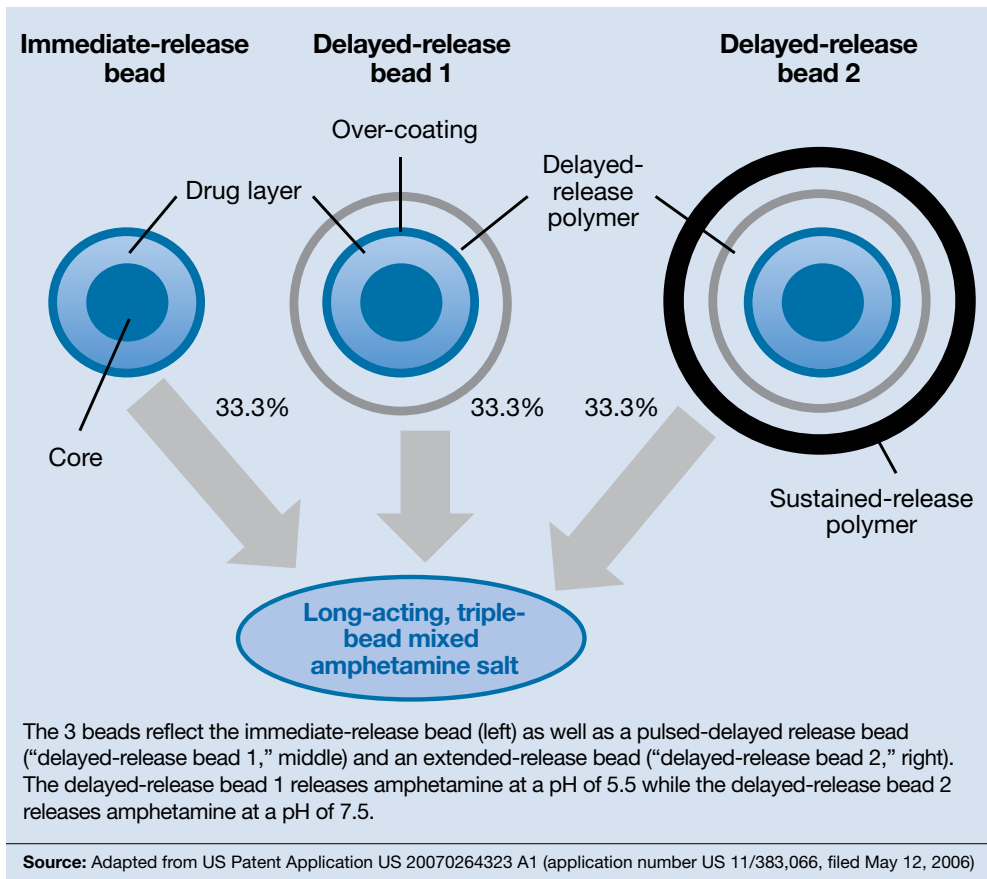
The preparation contains 3 MAS beads, resulting in a unique pharmacokinetic profile

Clinical Point

In CYP2D6 poor metabolizers, medication exposure may be increased

Figure 1

Mixed amphetamine salt is released via a 3-bead system, with each bead representing one-third of the drug



monoamine neurotransmitters. Additionally, amphetamine salts may inhibit the activity of monoamine oxidase (MAO), further increasing synaptic levels of monoamines.⁴ Enhancing noradrenergic, dopaminergic neurotransmission, particularly within the prefrontal cortex, increases attention, working memory, and processing speed in patients with ADHD.⁴

Pharmacokinetics

Cmax occurs approximately 7 to 10 hours and 8 hours following administration in adolescent and adult patients, respectively (*Figure 2, page 35*).³ In adolescents who were administered a single dose of long-acting, triple-bead MAS, Cmax and area under the curve (AUC) for d- and l-amphetamine were both 21% to

31% higher compared with adults³ and did not appear to be affected by sex or race.³

Half-life is 10 to 11 hours for d-amphetamine and 10 to 13 hours for l-amphetamine and does not statistically differ between pediatric and adult studies.³

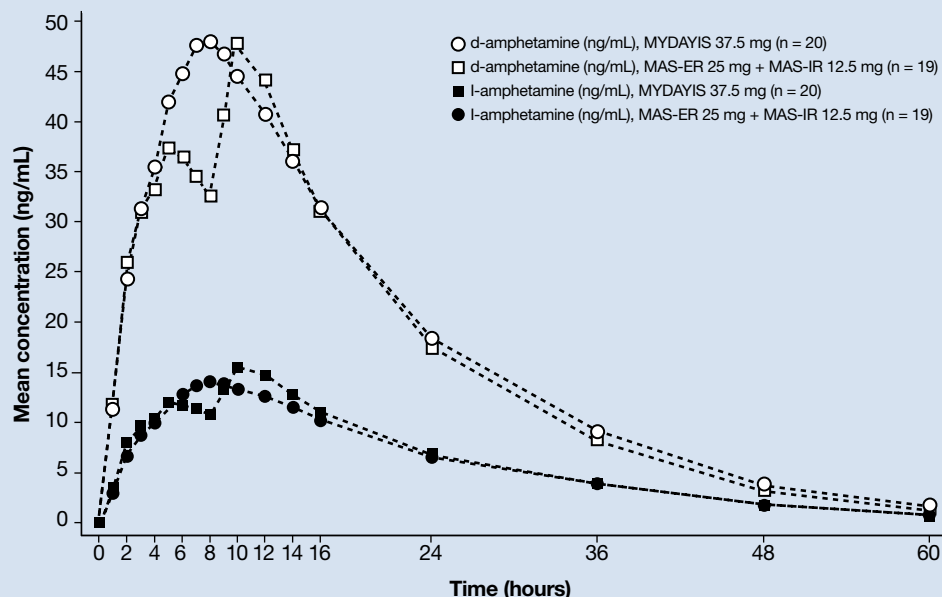
Metabolism and elimination. Amphetamines are partially metabolized through cytochrome 450 (CYP) 2D6-dependent mechanisms, and thus in CYP2D6 poor metabolizers medication exposure may be increased, while decreased exposure may occur in ultra-rapid metabolizers; however, there are no guidelines from the Clinical Pharmacogenetics Implementation Consortium regarding alternate dosing strategies for patients based on CYP2D6 genotype or activity phenotype.⁵ Because



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Figure 2

Release of long-acting, triple-bead mixed amphetamine salt preparation based on pharmacokinetic data contained in the prescription drug label



Administration of a 37.5-mg dose results in similar exposure compared with an extended-release form of mixed amphetamine salts (25 mg), followed by a 12.5-mg dose of immediate-release mixed amphetamine salt, administered 8 hours later.

Source: Reference 3

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In adults, titration should occur in 12.5-mg weekly increments to a maximum dosage of 50 mg/d

amphetamines are renally excreted, dosages should be adjusted in patients with renal impairment.

Drug interactions. Medications that affect gastrointestinal and urinary pH may affect serum concentrations of amphetamine. Specifically, agents that increase gastric pH (eg, proton pump inhibitors) as well as urinary alkalinizing agents (eg, acetazolamide, some thiazide diuretics) increase serum amphetamine concentrations.³ Because amphetamine is a weak MAOI, there is a theoretical risk of serotonin syndrome when amphetamine-based preparations are used concurrently with SSRIs, TCAs, and MAOIs. However, the concurrent use of MAS and SSRIs generally is considered safe and common practice in patients with ADHD and co-occurring anxiety^{6,7} or depressive disorders.

Dosing

Long-acting, triple-bead MAS is available in 12.5-, 25-, 37.5-, and 50-mg capsules. The capsule may be opened and sprinkled in food for patients who cannot swallow capsules. Opening of the capsule results in similar absorption relative to oral administration of the intact capsule.³

In adults with ADHD, long-acting, triple-bead MAS should be initiated at 12.5 mg in the morning (*Table 2, page 36*). However, in some individuals, long-acting, triple-bead MAS may be initiated at 25 mg each morning. Titration should occur in 12.5-mg weekly increments to a maximum dosage of 50 mg/d.³

In adults with severe renal impairment (glomerular filtrate rate, 15 to 30 mL/min/1.73 m²), the recommended starting

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Statistically significant, clinically relevant improvement was observed with triple-bead MAS compared with placebo

Table 2

Dosing for long-acting, triple-bead mixed amphetamine salt formulation

Recommended starting dose	Titration schedule		Maximum daily dose
Adults	12.5 mg	12.5 mg weekly	50 mg
Adolescents (ages 13 to 17)	12.5 mg	12.5 mg weekly	25 mg

Source: Reference 3

dose is 12.5 mg/d, with a maximum dosage of 25 mg/d.³

The efficacy of long-acting, triple-bead MAS in adults with ADHD was demonstrated in 3 studies involving adults ages 18 to 55, and the effectiveness of the medication, with regard to duration of action, was assessed using the Time-Sensitive ADHD Symptom Scale—a self-report scale that consists of items indexed by the ADHD Rating Scale-IV (ADHD-RS-IV) which assesses ADHD symptom severity. Doses up to 75 mg/d were studied; however, there were no significant effects. It should be noted that this maximum daily dose was not determined by any safety parameter.

Study 1 (dose-optimization, triple-bead MAS, n = 137; placebo, n = 135, dosing: 12.5 to 75 mg) and Study 2 (forced dose-titration study, triple-bead MAS, n = 308; placebo, n = 104, dosing: 25 mg, 50 mg, 75 mg) demonstrated efficacy of triple-bead MAS for treating ADHD in adults. Despite differences in study designs, statistically significant and similar clinically relevant improvement was observed with triple-bead MAS (vs placebo) on ADHD-RS-IV total scores in both Study 1 and Study 2.⁸ An additional study in adults ages 18 to 55 (N = 275) with ADHD (DSM-5 criteria) involved randomization to either 12.5 mg (fixed dose) or forced titration (12.5 to 37.5 mg) or placebo and, as with the first 2 studies, improvement in ADHD symptoms was observed in triple-bead MAS-treated patients relative to those who had received placebo. (See Reference 3 for a summary of the clinical trials of triple-bead MAS in adults with ADHD.)

The tolerability of this medication was evaluated in a 12-month open-label study of adults with ADHD (DSM-IV-TR criteria) in

which discontinuation was higher at doses >25 mg/d.⁷ Treatment-related increases in blood pressure and heart rate were consistent with the known hemodynamic adverse effect profile of stimulants.⁹

In adolescents with ADHD ages 13 to 17, long-acting, triple-bead MAS should be initiated at 12.5 mg/d and may be increased to 25 mg/d (Table 2). Importantly, in younger patients, including those younger than age 12, triple-bead MAS was associated with an increased risk of adverse events including insomnia and anorexia, and this was thought to be related to increased drug exposure (ie, AUC).

The efficacy of long-acting, triple-bead MAS was evaluated in 2 studies of adolescents ages 13 to 17, including 1 fixed-dose trial (25 mg/d) and 1 flexibly-dosed trial (12.5 to 25 mg/d). These unpublished studies utilized the ADHD-RS-IV score and the Average Permanent Product Measure of Performance, an age-adjusted math test and measure of sustained attention, and revealed statistically significant differences between medication and placebo in the primary outcomes.³

Adverse effects

Long-acting, triple-bead MAS was developed to treat ADHD symptoms throughout the day, and serum concentrations of the medication may be higher with this formulation compared with other long-acting preparations. Therefore, adverse effects that are directly related to plasma exposure (eg, insomnia and appetite suppression) may occur at higher rates with this preparation compared with alternatives. For example, in some of the registration trials, insomnia occurred in more than one-third of patients

receiving the active medication (38%).⁹ Although insomnia was the most frequently reported adverse event in adults with ADHD, most reports of insomnia occurred early in the course of treatment. Of these insomnia-related adverse events, 94% were mild to moderate and resulted in discontinuation of the medication in approximately 2% of patients. Further, 73.9% of treatment-emergent, insomnia-related adverse events resolved during the course of the study. It is also important to note that the Pittsburgh Sleep Quality Index did not differ from placebo in studies of triple-bead MAS in adults with ADHD.¹⁰ Similarly, rates of stimulant-induced appetite suppression may be higher with this preparation compared with other long-acting preparations.⁹

Adverse effects observed in adults with ADHD that occurred in $\geq 2\%$ of patients receiving triple-bead MAS and at least twice the incidence in patients randomized to placebo included:

- anxiety (7% vs 3%)
- feeling jittery (2% vs 1%)
- agitation (2% vs 0%)
- insomnia (31% vs 8%)
- depression (3% vs 0%)
- decreased appetite (30% vs 4%)
- weight loss (9% vs 0%)
- xerostomia (23% vs 4%)
- diarrhea (3% vs 0%)
- increased heart rate (9% vs 0%)
- palpitations (4% vs 2%)
- dysmenorrhea (4% vs 2%)
- erectile dysfunction (2% vs 1%).

In adolescents receiving triple-bead MAS, the most common adverse effects included

Related Resource

• Parikh AR, Baker SA. Adult ADHD: pharmacologic treatment in the DSM-5 era. *Current Psychiatry*. 2016;15(10):18-25.

Drug Brand Names

Acetazolamide • Diamox	Mixed amphetamine salt (immediate-release) •
Lisdexamfetamine • Vyvanse	Adderall
Long-acting, triple-bead mixed amphetamine salt • Mydayis	Mixed amphetamine salt (extended-release) • Adderall XR

decreased appetite, nausea, insomnia, abdominal pain, irritability, and weight loss.⁹

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Clinical Point

In younger patients, triple-bead MAS was associated with an increased risk of insomnia and anorexia

Bottom Line

Long-acting, triple-bead mixed amphetamine salt (MAS) for attention-deficit/hyperactivity disorder is well tolerated. Published trial data demonstrate a longer duration of action than other preparations of MAS-based formulations; however, because of its long duration of action, this preparation may be associated with more insomnia and appetite suppression than other MAS formulations.