

New Options in the Pharmacological Management of Attention-Deficit/Hyperactivity Disorder

Mark Olfson, MD, MPH

Abstract

A brief review of the efficacy and common side effects of pharmacological treatments for attention-deficit/hyperactivity disorder (ADHD) is presented. Methylphenidate and amphetamine continue to have the strongest base of empiric support. They are both available in extended- and immediate-release preparations. Although most children with ADHD respond favorably to either medication, many children who do not respond to one medication will respond to the other. Additional pharmacological options include the nonstimulant atomoxetine, the stimulant pemoline, the antidepressants bupropion and desipramine, and the antihypertensives clonidine and guanfacine. In selecting the appropriate pharmacological regimen, consideration should be given to the child's daily school and after-school schedule, the presence of aggressive symptoms, and the risk of diversion. Careful selection of an appropriate medication regimen and active engagement of the child, parents, and teacher in daily management may help to ensure long-term adherence.

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Each year in the United States, an estimated 3.0% of children aged 3 to 18 years receive pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD).¹ This overall rate of treatment is at the lower end of the range of community prevalence estimates for ADHD (3%-5%) among school-age children.²⁻⁴ Across individual communities, however, there is probably substantial variation in the rate and quality of pharmacological treatment of ADHD. Whereas 1 study of 4 communities found that one eighth of children diagnosed with ADHD received adequate pharmacological treatment,⁵ a second survey of a rural region reported that a substantial proportion of school-age children who received pharmaco-

logical treatments for ADHD did not meet clinical criteria for the disorder.⁶ In 2 communities, elementary school children were reported to be prescribed pharmacological therapy for ADHD at 2 to 3 times the expected base rate prevalence of the disorder.⁷ Such findings suggest that substantial variation exists in the extent and quality of pharmacological treatment as well as the diagnosis of ADHD in the United States.

Stimulant medications are the mainstay pharmacological treatment for ADHD. Stimulants, which include methylphenidate (MPH), amphetamine (AMP), and pemoline, are prescribed to more than 80% of outpatients treated for ADHD.¹ More experimental evidence supports the safety, dosing, and efficacy of stimulants than any other psychopharmacological treatment for children.⁸ Among the stimulants, MPH is by far the most commonly prescribed medication.

There is a nearly 70-year history of treatment of hyperactive children with stimulants. In the past several years, substantial progress has been made in broadening the range of pharmacological choices to manage ADHD. What follows is a brief review of the efficacy of drug treatments focusing on new stimulant preparations and other new pharmacological options.

Efficacy of Stimulants

Controlled clinical trials consistently demonstrate that treatment with stimulants substantially reduces the characteristic symptoms and impairment of patients with ADHD.⁹⁻¹¹ Stimulants result in a rapid improvement in the conduct, attentiveness, and academic performance of children and adolescents with ADHD.⁹ Approximately

70% of ADHD patients respond to stimulant medications in the short term¹⁰ and over periods up to 18 months.^{11,12} In addition to pharmacological treatments, which are the focus of the current review, behavioral approaches involving classroom behavior modification and academic interventions,^{13,14} parent training,¹³ contingency management programs,¹⁵ and special education placement¹⁶ are also established treatments for children with ADHD. For some patients in some outcome domains, medications in combination with behavioral psychosocial interventions may be more effective than either treatment alone. In the National Institute of Mental Health (NIMH) Multimodal Treatment Study of ADHD (MTA), for example, patients who received the combined treatment significantly improved on a composite measure that combined ADHD symptoms and other functioning domains, in relation to those who received either medication management or behavioral treatment alone.¹⁷ However, the effect sizes were modest. For ADHD symptom outcomes, patients receiving combination strategy and medication management alone did not meaningfully differ in improvement, and both groups achieved significantly greater symptom reduction than the behavioral-treatment-alone group.

Studies comparing the efficacy of MPH, AMP, and dextroamphetamine (DEX) have generally failed to show group differences in key outcomes.¹⁸ Most young people respond well to each medication. However, individual patients may vary substantially in their clinical response to the different medications and to different doses of the same medication.¹⁹ Unfortunately, there are no physiological or psychological measures that reliably predict response to individual stimulants. However, controlled crossover studies indicate that a substantial proportion of children with ADHD who do not respond to MPH, respond favorably to AMP and conversely a substantial proportion of AMP nonresponders respond to MPH.^{20,21}

Dexmethylphenidate (Focalin) is the pharmacologically active D-threo enantiomer of MPH. Although the L-isomer is more rapidly metabolized and degraded than the D-isomer following oral administration,

the L-isomer has little or no clinical efficacy. In a randomized, double-blind, controlled trial comparing twice-daily dexmethylphenidate, immediate-release MPH, and placebo, both active drugs were significantly more efficacious than placebo, according to teacher and parent ratings of ADHD symptoms. There was also a trend favoring dexmethylphenidate, based on evening ratings.²² Dexmethylphenidate is typically prescribed at one half the dose of the usual racemic MPH mixtures. At present, dexmethylphenidate is only available as an immediate-release formulation.

Development of Long-acting Stimulants

Standard stimulants have a relatively brief duration of action.²³ The clinical effects of the immediate-release preparations of MPH, DEX, and mixtures of AMP occur during the first 30 minutes following dosing, reach maximal effect over approximately 2 hours, and are no longer clinically apparent at 5 hours.²⁴ The short duration of action of immediate-release preparations represent an important limitation to their effectiveness in community practice.

The clinical effects of pemoline last for up to 6 hours. However, abnormal elevations in serum hepatic enzymes occur in 1% to 3% of youth receiving maintenance pemoline treatment.²⁵ Together with rare reports of pemoline-related fatal hepatic toxicity, these findings have led to a warning concerning hepatic toxicity in the medication's package insert.²⁵ As a result, pemoline is not generally regarded as a first-line treatment for ADHD.

For continuous coverage with immediate-release formulations of MPH throughout the day, school-age patients must receive at least 1 dosage during school. A typical regimen of immediate-release preparations involves a dose at breakfast (8:00 AM), another at lunch, and a third dose after school to provide coverage for homework and other after-school activities. The necessity for in-school dosing risks embarrassing the student in front of his or her peer group. A school nurse or other school staff member is also generally required to dispense the midday stimulant dose. Because some schools may not reliably administer midday dosages and other

schools may prohibit administration of medications altogether, immediate-release preparations may pose problems with long-term treatment adherence. In addition, children may simply forget to take their medication, especially the after-school dose. In one 12-month retrospective study of once-daily osmotic release oral system (OROS) MPH (Concerta), patients were less likely to switch to other medications when compared to patients taking short- and intermediate-acting MPH treatments.²⁶ Further, a 9-month healthcare claims data study assessing persistency with therapy suggests that patients prescribed OROS MPH were 42% more likely to persist on their medication than those prescribed ER (extended-release) MPH.²⁷

Sustained-release formulations of MPH and DEX represent advances in the pharmacological management of ADHD. The sustained-release preparations provide continuous clinical effects throughout the traditional 8-hour school day. This extended coverage eliminates the requirement of in-school-administered dosing.²⁸ Because early treatment termination is quite common in the community care of ADHD²⁹⁻³¹ and because less complex dosing regimens are generally associated with improved adherence,³² sustained-release formulations are believed to have facilitated stimulant medication adherence in community practice.

MPH-20 (Ritalin-SR) was one of the earliest long-acting stimulants. It relies on a wax-matrix vehicle to release the medication slowly following ingestion. There are now several slow-release racemic MPH generic preparations that use a similar wax-matrix vehicle. However, clinicians and experts report that such extended-duration preparations are less effective, especially by the afternoon, than standard 3-times-daily dosing of immediate-release MPH.³³ This may be because immediate-release MPH preparations produce higher peak plasma concentrations with a steeper absorption slope than the slow-release, long-acting preparations.³⁴ The performance of children may be enhanced by a rising rather than steady plasma concentration of MPH.³⁵ Similarly, although long-acting DEX formulations have a typical duration of approximately 8 hours, these medications may not achieve pro-

longed behavioral effects because of the steady concentrations.³⁶

OROS MPH is a new single-daily-dose MPH preparation that retains the increased efficacy associated with immediate-release MPH. Following ingestion of an OROS MPH tablet, there is an immediate release of MPH in the outer covering of the tablet. After this initial bolus, there is a slower controlled release of MPH over approximately 8 hours. As water permeates the semipermeable tablet covering, MPH is released into the bloodstream through a laser-drilled hole at one end of the capsule that acts as an osmotic pump.³⁷ In a large randomized controlled trial, OROS MPH once per day was as effective as MPH immediate release given in the standard 3-times-daily regimen.³⁸ A recently published open-label study further suggests that clinical improvements achieved with OROS MPH are generally sustained over the 12-month follow-up period of continuous treatment.³⁹

MPH hydrochloride (Metadate CD) is another sustained-release MPH formulation. The capsule combines 30% of immediate-release MPH and 70% ER MPH beads. This formulation typically results in a peak plasma concentration approximately 1.5 hours after dosing and a second peak approximately 4.5 hours after dosing. Metadate CD has the advantage that it can be given as a sprinkle over food. This may be especially helpful in the treatment of younger children who are unable to swallow a pill.

Adderall (dextroamphetamine saccharate/dextroamphetamine sulfate/amphetamine aspartate/amphetamine sulfate) is a mixture of 75% DEX and 25% levoamphetamine. The clinical duration varies from 5 to 8 hours depending on dose, absorption, and metabolism. A randomized, double-blind, controlled trial comparing ER DEX spanules and immediate-release DEX revealed that both immediate-release preparations had earlier onset of effects, while the spanule preparation had more sustained clinical effects.⁴⁰

Adderall XR, a recently marketed ER mixed amphetamine salts (MAS XR), uses a bead technology to provide a double-pulsed delivery of immediate-release MAS. One half of the active ingredient is released upon

ingestion and the other half is released approximately 4 hours later. The clinical duration of MAS XR is intended to replicate a 4-hour, twice-daily dosing of immediate-release Adderall (MAS). Some research suggests the effects of a single morning dose of MAS XR extends beyond the 8-hour school day to 10 or 12 hours.

Adverse Effects, Contraindications, and Longer-term Risks of Stimulants

Most side effects experienced by children treated with stimulants for ADHD are relatively mild, time-limited, and resolve following adjustment of the dose or daily regimen. The most common adverse events early in the course of stimulant treatment of children with ADHD include difficulty falling asleep, reduced appetite, stomachache, headache, and dizziness.⁴¹ Although pediatricians commonly reduce or eliminate the after-school dose of MPH to reduce insomnia, it is not clear that this dose of immediate-release MPH contributes to sleep difficulties.⁴²

The package insert for each stimulant medication lists specific contraindications, warnings, and precautions. From a clinical perspective, the most significant contraindications include concomitant treatment with a monoamine oxidase (MAO) inhibitor and stimulant treatment of patients with psychotic disorders or glaucoma. Although MAO inhibitors are rarely used in contemporary clinical practice, there is a contraindication concerning their use in patients treated with stimulants. MAO inhibitors taken with stimulants may trigger severe hypertension and increase the risk of cerebrovascular accidents. Stimulants should also be avoided in patients with a known history of schizophrenia, schizoaffective disorder, mania, or other psychotic disorders. In patients with psychotic disorders, stimulants may trigger exacerbations of psychotic symptoms. Sympathomimetic agents, including stimulants, may increase intraocular pressure and should be avoided in patients with glaucoma.

Patients with a history of stimulant abuse or dependence should also not be treated with stimulants. Because parents and other family members may abuse stimulants prescribed for someone else in the family, a careful family history of substance abuse is

warranted before a physician prescribes stimulant therapy. Although there is wide acceptance of the need to avoid stimulant treatment in patients with a history of stimulant or polysubstance abuse, controversy surrounds the extent to which stimulant use leads to abuse or dependence in young people without a history of these disorders. Some investigators report that stimulants differ in their ability to induce euphoria, with DEX having the highest liability, MPH an intermediate liability, and pemoline possessing little or no euphorogenic potential.^{43,44}

Stimulants may not be the only cause for increased substance abuse for ADHD patients. ADHD, by its nature, may have an impact on increasing the risk of substance use disorders. A recent and controversial meta-analysis of 6 studies of adolescents and young adults suggests that contrary to these concerns, stimulant therapy in childhood is actually associated with a reduction in subsequent substance use disorder.⁴⁵ One explanation for earlier reports linking stimulant treatment to substance abuse is failure to control for the potentially confounding effects of comorbid conduct disorder that increase risk of substance abuse.^{46,47} Continued research in this important area is warranted.

Some individuals with a history of intravenous drug abuse may attempt to dissolve tablets of stimulants before injecting them intravenously. This practice poses risks of pulmonary talc granulomatosis and pulmonary hypertension.⁴⁸ Stimulant abuse also sometimes involves crushing and intranasally inhaling the drug. OROS MPH is less prone to these forms of abuse than immediate-release MPH preparations because it exists as a pasty substance that cannot be injected or snorted.⁴⁹

Controversy surrounds the extent to which long-term stimulant treatment of children slows their height and weight growth. While some studies show significant attenuation of growth on stimulants,^{50,51} others show only small effects.^{52,53} Catch-up in growth may be inferred from cross-sectional studies that demonstrate that the heights of adults treated as children with stimulants do not significantly differ from controls.^{54,55} Given the uncertainty regard-

ing the effects of long-term stimulant treatment on growth rates, it is prudent for clinicians to monitor carefully the height and weight of treated children with regular measurements plotted on growth charts.

Nonstimulants

Atomoxetine (Strattera) is a nonstimulant for the treatment of ADHD approved by the US Food and Drug Administration. It enhances noradrenergic function through highly selective and potent inhibition of the presynaptic reuptake of norepinephrine. Low concentrations of norepinephrine in the right dorsal and orbital sections of the prefrontal cortex are believed to contribute to many ADHD symptoms.⁵⁶ Controlled trials have demonstrated that atomoxetine is more efficacious than placebo in the treatment of children and adults with ADHD. The adverse effects and discontinuation rates associated with atomoxetine appear to resemble those of MPH. However, atomoxetine may not have the abuse potential of MPH because it does not affect the nucleus accumbens or striatum, regions of the brain implicated in addictive behaviors.⁵⁷ Although stimulants remain the first-line treatment for ADHD, atomoxetine is an efficacious alternative for patients who do not respond to stimulants or do not tolerate them.

Several other medications have been studied for their efficacy in ADHD. Among the most extensively studied are the tricyclic antidepressants imipramine and desipramine. These medications effectively inhibit norepinephrine reuptake and have been demonstrated to be more effective than placebo in controlled clinical trials of the treatment of ADHD. However, because imipramine and desipramine affect cardiac conduction, and therefore require periodic electrocardiograms and blood drug level monitoring, they are rarely used for the treatment of pediatric ADHD.

The antidepressant bupropion (Wellbutrin) is also efficacious in the treatment of pediatric ADHD.^{58,59} Because improvement with bupropion treatment is generally not as robust as improvement with stimulants,⁶⁰ it is also seldom used as a primary treatment for ADHD, though it is used more common-

ly as an adjunctive agent. There is also evidence that the antihypertensives clonidine⁶¹ and guanfacine⁶² are effective in reducing some ADHD symptoms in children. However, concerns about hypotension, rebound hypertension, and sedation have limited their use in clinical practice.

Pharmacological Management of Patients With Comorbid Mental Disorders

Youth with ADHD commonly have co-occurring mental disorders. In the large NIMH MTA study of ADHD, for example, 40% of the subjects had oppositional defiant disorder, 39% had an anxiety disorder, 14% had conduct disorder, 11% had a tic disorder, and 4% had a mood disorder.¹⁷ In addition, adolescent and adult ADHD may contribute to the development of substance use disorders.⁶³ The presence of comorbid mental disorders complicates the pharmacological treatment of ADHD. Although a detailed examination of this broad and complex topic is beyond the scope of the current review, a brief discussion is provided on pharmacological treatment of ADHD with comorbid tic disorders and ADHD with aggressive behavior common in oppositional defiant and conduct disorders.

Case reports have long fueled concern that stimulants exacerbate tic disorders in children with ADHD. However, prospective studies indicate that stimulants are generally safe and effective for the treatment of ADHD in most children with mild-to-moderate comorbid tic disorders.^{64,65} In children with both disorders whose ADHD symptoms do not respond or whose tics worsen following stimulant therapy, some evidence supports treatment with desipramine⁶⁶ or guanfacine.⁵⁶ One randomized, controlled trial of children and adolescents with both disorders demonstrated that, as compared with placebo, desipramine (3.4 mg/kg/day) significantly reduced core ADHD symptoms and tic symptoms.⁶⁶ Similarly, a randomized, controlled trial revealed that as compared with placebo, the α_2 -adrenergic receptor agonist guanfacine (1.5-3.0 mg/day) significantly reduced total ADHD and tic symptom scores. In this study, however, guanfacine was not associated with a significant decline in parent-rated hyperactivity.⁶⁷

Stimulants are only modestly effective in reducing aggressive behavior in young people with ADHD.⁶⁷ Some evidence suggests that clonidine augmentation of stimulant therapy is a safe and effective treatment for aggression in young people with ADHD.^{68,69} In one randomized, controlled trial, children treated with a stimulant and clonidine as compared with stimulant alone exhibited a significantly greater reduction in conduct symptoms, but not in hyperactive symptoms. Children treated with clonidine and a stimulant generally experienced fewer side effects than the stimulant-only group, though they did experience a transient increase in dizziness and drowsiness. Although concern has been expressed regarding adverse cardiovascular events including sudden death in children treated with clonidine and a stimulant,⁷⁰ no serious cardiovascular events occurred in this study.

Conclusion

Widespread variation exists in the rate and quality of pharmacological treatment for ADHD.^{5,6,71} Extending the initial evaluation to include a thorough symptom and functional assessment of the child and soliciting a detailed history from parents and teachers may improve the accuracy of the diagnostic process.⁷² Once a diagnosis is established, appropriate selection of pharmacotherapy requires a knowledge of available pharmacological treatments and an understanding of daily coverage needs of the child.

Available stimulant preparations offer a range of pharmacokinetic profiles and durations of action to help meet the diverse and changing needs of ADHD patients over time. The long-acting medications may enhance medication adherence by obviating the need for a midday stimulant dose in school and reducing the need for a dose after school. Children who do not respond to one stimulant medication may respond to another stimulant or to the nonstimulant atomoxetine. Long-acting preparations and atomoxetine may also reduce the potential for related drug abuse.

Stimulant medications provide short-term behavioral and academic improve-

ment. To maintain these benefits, many children must remain on these medications over the long term. Simplifying the pharmacologic regimen and selecting the medication regimen that best meets the child's needs may contribute to improved clinical outcomes. In addition, healthcare professionals should provide children, parents, and teachers with appropriate information about pharmacological therapy and treatment response to increase their participation in the treatment process. Although the duration of treatment with stimulants is increasing,⁹ early treatment discontinuation remains common.⁷³ Older patient age, comorbid oppositional defiant disorder, and fewer ADHD symptoms may place young people with ADHD at particular risk of medication nonadherence.⁷⁴

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