NEW ADHD TREATMENT OPTIONS ON THE HORIZON*

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders of childhood, yet there have been historically few pharmacologic treatment options available. Methylphenidate was introduced in 1958, and has been the mainstay of treatment for several decades. Although safe and effective, a short duration of action and side effects common to stimulants have been problematic for some patients requiring treatment. Recent technological advances in delivery systems will afford many patients the option of fewer doses throughout the day. Efforts have also focused on developing nonstimulant treatment options for ADHD, as some patients either do not respond or cannot tolerate stimulants. This article will review recent developments in delivery systems for the stimulant medications, as well as nonstimulant treatment options under development.

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The treatment of attention-deficit/hyperactivity disorder (ADHD) is multifaceted. Providers must work with the patient and the family to identify goals for treatment to target specific symptoms. Once goals have been established, it naturally follows that function and performance in achieving goals should be monitored, and that overall ADHD *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV) symptoms be monitored as well.

Within this framework, medication management is an important aspect of overall treatment, as was clearly demonstrated by the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder,[1] the largest federally funded study of child psychiatry. In the study, a group of the 579 children with ADHD combined type, aged 7 to 9.9 years, were assigned to 1 of 4 treatment arms over a 14-month period. The study compared outcomes for children across 4 study arms: medication management supervised by providers with significant experience treating children with ADHD; comprehensive behavioral treatment, which engaged parents and caseworkers in carrying out targeted interventions in the home and at school; combined medication management and intensive behavioral treatment; and treatment from community providers.

Across all 4 groups, symptoms were significantly reduced over time. However, the degrees of change varied significantly across groups. It is particularly telling that the community-care group did not fare well in the study, which addresses that, as providers, we need to further educate ourselves regarding the treatment of ADHD and the appropriate interventions. The study did stress, however, the important

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role of medication, which would be expected given the medical evidence suggesting that ADHD is a neurobiological disorder. Specific findings of the study demonstrated that children who underwent medication management, with or without behavioral intervention, showed significantly greater improvement than those given intensive behavioral treatment and community care without medication. Outcomes for the combined study arm and the medication management study arm were similar. Not surprisingly, study providers within the medication management arm who had extensive experience treating ADHD had superior outcomes to those reported for community providers, even though they frequently prescribed medication management. Such findings suggest that while medication is effective, it is more effective when administered by those with specific knowledge of ADHD treatment modalities.

Stimulant Medications

Stimulant medications are among the most robust treatments available in psychiatry, far outpacing success rates achieved with antidepressants, antipsychotics, and mood stabilizers. As many as 70% of children with ADHD will respond to any of the available stimulants, which generally are all of equal efficacy. An additional 20% will respond to a second stimulant should the first prescribed drug fail to achieve any significant change in symptoms, so that 90% of children with ADHD will respond to one of the first treatments selected. If the switch in therapy does not achieve results, providers then must reevaluate the diagnosis to ensure that symptoms are in fact attributable to ADHD and not to a different disorder or an undiagnosed comorbidity.

The 2 primary stimulants, amphetamine and methylphenidate (MPH), have been used since 1937 and 1957, respectively. Thus, a tremendous amount of data has been collected regarding safety and efficacy for this drug class. Historically, one limitation of stimulant drugs was their short-acting profile, with MPH and dextroamphetamine lasting approximately 3 to 4 hours. D,l-amphetamine is a mid-range stimulant that lasts 5 to 7 hours. Newer stimulant medications include extended-release d,l-amphetamine with a 10- to 12-hour action profile, and the biphasic MPH class drugs whose actions extend for 8 hours and 12 hours. The mechanism of drug delivery is designed to release an initial dose, then to delay release of additional doses, so that 2 or more doses of drug are delivered across extended time intervals. The most recently released drug in the methylphenidate armamentarium is d-methylphenidate, a single isomer of MPH with a 3- to 4-hour duration of action. Because the l isomer component has been extracted, the drug delivers half the dose of standard MPH.

Alternatives to Stimulants

Although the safety and efficacy of stimulants for the treatment of ADHD is widely documented, investigation of additional options continues for a number of reasons. In some cases, stimulant use has been linked to decreased appetite and delayed sleep onset. Although longer-lasting formulations are now available, the time-action profile at best is 12 hours. Moreover, stimulants are Schedule II classified drugs, and the potential for diversion and abuse exists. From a physician's standpoint, the classification is somewhat troublesome in that refills are not permitted, prescriptions may not be called into the pharmacy, and the provider may not offer drug samples to patients. Finally, although generally highly effective, stimulants, like all drugs, simply are not effective in some patients.

Although alternatives to stimulants are available, none has US Food and Drug Administration (FDA) approval for use in ADHD. Desipramine and other tricyclics, for example, widely used in the treatment of depression, have also been shown to be very effective in treatment of ADHD; however, issues regarding the drug's tolerability and cardiac impact have been raised.[2] Tricyclic antidepressants can cause weight gain, sedation, dry mouth, constipation, and other anticholinergic effects, as well as slowing of cardiac conduction. Bupropion has shown some efficacy in the treatment of ADHD, although it is not FDA approved for that indication. Clonidine and guanfacine have demonstrated some benefits in treatment of hyperactivity, but are believed to be less efficacious with inattention problems.[3]

Atomoxetine is an investigational agent currently being evaluated by the FDA. It is a potent inhibitor of the presynaptic norepinephrine transporter (K_i 4.5 nM), with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. Atomoxetine's clinical profile seems to differ from that of stimulants,[4] and it is being studied as a treatment for ADHD. More than 4000 children, adolescents, and adults have taken atomoxetine during rigorous short- and long-term clinical trials. Among the first analyses of the effectiveness and tolerability of

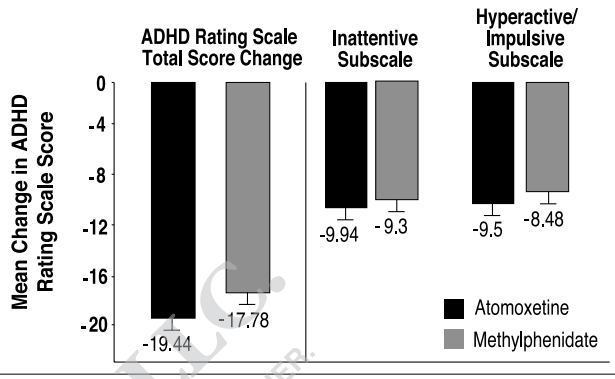
atomoxetine in adults with ADHD was a double-blind, placebo-controlled, crossover study of atomoxetine in 22 adults with well-characterized ADHD.[5] Following an average dose of 76 mg, 11 of 21 patients showed improvement, compared with only 2 of 21 patients who improved after receiving placebo.

This initial trial has been followed by a series of larger studies assessing the efficacy and safety of atomoxetine in children and adolescents with ADHD. The first was a prospective, open-label trial to assess the efficacy of atomoxetine versus MPH in children aged 7 to 15 years who met DSM-IV criteria as determined by the Kiddie-Schedule for Affective Disorders and Schizophrenia (KSADS), with scores on the ADHD-IV rating scale of 1.5 standard deviation above age/gender norms.[6] Excluded from the study were children with a history of bipolar or psychotic disorder, substance abuse, or who failed to respond to previous MPH treatment. Atomoxetine, given to 184 study subjects, was titrated to a maximum dose of 2 mg/kg/day and dosed before and after school. In the MPH study arm, 44 subjects initially received 5 mg (1-3 times/day), dosed to a maximum of 60 mg/day. Following a 1-week "washout" screening and evaluation period, over a 20-week period subjects in the atomoxetine study arm showed a 19-point reduction in ADHD Rating Scale total scores, versus an 18-point reduction in total scores for the MPH study arm. Similar reductions occurred in the inattentive symptoms as well as with hyperimpulsive symptoms (Figure 1).

To date, 3 placebo-controlled multisite studies of atomoxetine have been completed: 2 identical dose-titration studies (Spencer et al, in review), and 1 dose-response study.[7] Findings have been similar among all 3 studies, with atomoxetine demonstrating statistically superior results to placebo. In the dose-response study, the relationship between dose and symptom change was evaluated in 297 outpatients with ADHD, aged 8 to 18 years. Subjects were randomized to placebo or atomoxetine dosed on a weight-adjusted basis at 0.5 mg/kg/day, 1.2 mg/kg/day for an 8-week period.

At endpoint, atomoxetine 1.2 mg/kg/day and 1.8 mg/kg/day were consistently associated with superior outcomes in ADHD symptoms compared with placebo (Figure 2). The study showed that at a dose of approximately 1.2 mg/kg/day, near-maximum efficacy was achieved in ADHD

Figure 1. Change in Efficacy Outcomes: ATMX vs MPH



P<.001 within treatment group, baseline to endpoint
P = NS between groups.
ATMX = atomoxetine; MPH = methylphenidate.
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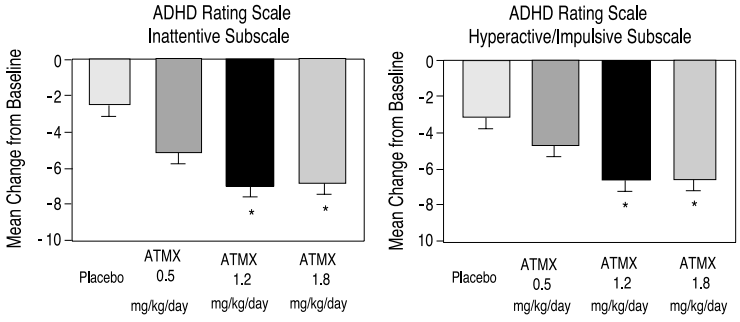
Figure 2. ADHD Rating Scale: Subscale Scores



*Pairwise test vs PBO, *P*<.001. Test for linear dose response *P*<.001.
ATMX = atomoxetine.
Adapted with permission from reference 7.

symptoms, although atomoxetine was well tolerated at all doses. At 1.2 mg/kg/day, atomoxetine seemed to be as effective as 1.8 mg/kg/day, and 1.2 mg/kg/day is likely to be the appropriate initial target dose for most patients should the drug gain FDA approval and be released to market.

Although in early clinical trials atomoxetine was dosed on a twice-daily basis, once-daily dosing was investigated as part of the clinical development program to see if it was as effective and well tolerated as twice daily. Most patients do not accumulate atomoxetine during twice-daily dosing because of its 4-hour half-life; yet, atomoxetine has been noted clinically to be efficacious throughout the entire day. These findings suggest 2 possibilities: (1) therapeutic effects persist after the drug is cleared so that there is not a coupling of the therapeutic effect and the pharmacologic effects of the receptor; and (2) brain kinetics differ from plasma kinetics. Additional study is needed in this area. Results from the once-daily dosing study have been submitted for publication elsewhere and cannot be reported in detail at this time. However, results were positive, showing an effect size similar to twice-daily dosing with tolerability comparable to twice-daily dosing.

In regard to atomoxetine's acute safety profile, study data demonstrate results that would be expected with a noradrenergic drug: diastolic blood pressure increased ~3 mm Hg, and heart rate increased ~7 beats/minute. Weight decreased ~0.5 kg during acute therapy, usually throughout the first 9 to 12 weeks. No remarkable change in laboratory parameters was observed, and no clinically significant effects on QTc intervals have been observed to date.[8] The long-term safety study of atomoxetine, which extended to a 78-week period, demonstrated positive results. Among 325 study subjects, only 12 (3.7%) discontinued due to an adverse event. Consistent with findings of other studies, an increase from baseline to endpoint in mean diastolic blood pressure (3.6 mm Hg) and pulse (3.9 bpm) was observed. However, despite initial loss of appetite reported in shorter-term studies, mean weight increased (2.6 kg) from baseline to endpoint, as did mean height (4.4 cm).[9]

In summary, stimulants have proven to be very effective for the treatment of ADHD. Newer formulations with improved time-action profiles have been very useful for many patients. Though not yet approved for use in ADHD, atomoxetine is currently under investigation with results eagerly anticipated by the medical community.

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