



Treatment of Attention Deficit Hyperactivity Disorder: New Agents and Assessment Tools

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The currently available treatments for attention deficit hyperactivity disorder (ADHD), stimulants, alpha-2 adrenergic agonists, and atomoxetine, are highly effective in increasing attention and reducing impulsivity in most patients. Research continues to expand the range of treatment options, with new drugs and dosage formulations, as well as new methods to predict or assess treatment response.

Potential Treatment Options

Two novel ADHD medications are currently being studied in children and adults with ADHD. Edivoxetine, a selective norepinephrine reuptake inhibitor similar to atomoxetine, is in phase 3 trials. Both atomoxetine and edivoxetine are Eli Lilly products. Tipepidine, 3-[di-2-thienylmethylene]-1-methylpiperidine, is being studied in Japan. It has been available there as an over-the-counter cough suppressant since 1959. Tipepidine inhibits G-protein-coupled inwardly rectifying potassium-channel currents, resulting in increased levels of catecholamines in the brain.

Edivoxetine

The pharmacokinetic/pharmacodynamic profile, safety, and tolerability of edivoxetine were evaluated in a phase 1 open-label dose-ranging study of 53 children.¹ Patients were grouped according to weight to receive doses of 0.05, 0.1, 0.2, and 0.3 mg/kg. Pharmacokinetic parameters were similar in children and adolescents, with a mean time to maximum concentration of 2 hours and an elimination half-life of approximately 6 hours.

Forty-nine of the patients from this trial continued on into a subsequent open-label trial.² Patients received doses of 0.05-0.3 mg/kg once daily for a mean duration of treatment was 22 weeks. Statistically significant improvement was

seen in ADHD Rating Scale-IV (ADHD-RS-IV) total scores, with a mean change at endpoint of -17.6 ± 12.4 . Both hyperactivity/impulsivity and inattentive subscores improved, with a mean reduction of -8.8 for each. Global Impressions-ADHD Severity (CGI-ADHD-S) scores also demonstrated significant improvement from baseline. Adverse effects were typically mild, with the most commonly reported including nausea, decreased appetite, somnolence, and upper respiratory tract infections. The mean increase in systolic blood pressure was 1.9 mm Hg in children and 0.22 mm Hg in adolescents, with a mean change in heart rate of 3.5 bpm in children and 3 bpm in adolescents. Three patients discontinued treatment because of adverse effects. One patient experienced treatment-emergent mania, another developed signs of depression, and the third had consistently elevated blood pressures. There were no changes noted on the electrocardiograms.

A subsequent study was published in the May 2014 issue of *The Journal of Child and Adolescent Psychopharmacology*.³ This randomized, double-blind, placebo-controlled trial was conducted in 340 children 6-17 years of age. Patients were randomized to edivoxetine at a dose of 0.1, 0.2, or 0.3 mg/kg/day, placebo, or osmotic controlled-release oral delivery system (OROS) methylphenidate for the 8-week trial. The edivoxetine 0.2 and 0.3 mg/kg/day treatment groups had statistically greater improvement than placebo in ADHD-RS-IV scores (-16.09 and -16.39 versus -10.35, respectively, $p < 0.01$) and better Clinical Global Impressions scores (2.54 and 2.53 versus 3.05, $p = 0.013$). The effect size estimates in the stimulant-naïve arm were 0.17, 0.51, and 0.54 for the 0.1, 0.2, and 0.3 mg/kg/day for edivoxetine, compared to 0.69 for the methylphenidate. Edivoxetine produced a

small, but clinically significant increase in blood pressure and heart rate compared to placebo ($p < 0.05$). The authors concluded that edivoxetine at doses of 0.2 or 0.3 mg/kg/day demonstrated efficacy in the treatment of ADHD. Results from placebo-controlled trials of edivoxetine in adults have produced similar results.

Tipepidine

An open-label proof-of-efficacy pilot study of tipepidine in children with ADHD was recently published in *Neuropsychiatric Diseases and Treatment*.⁴ Ten children (mean age 9.9 years) received a dose of 30 mg/day for 4 weeks. Three of the patients were stimulant naïve; the remaining seven patients continued on their current regimen throughout the study. There was significant improvement in ADHD-RS-IV total scores, with a reduction from 30.2 ± 9.9 at baseline to 16.4 ± 8.4 at 4 weeks ($p < 0.001$). The mean hyperactivity/impulsivity subscore decreased from 11.2 ± 7.1 to 5.0 ± 4.1 and the inattentive subscore decreased from 19.0 ± 3.6 to 10.6 ± 3.8 ($p < 0.001$). Although not statistically significant, there was a trend towards improvement in Das-Naglieri Cognitive Assessment System scores. Adverse effects were mild, with no patients discontinuing treatment. There were no adverse effects on blood pressure or heart rate. Based on their results, the authors suggest that additional studies, including dose-escalation or dose-ranging trials, are warranted. They speculate that higher doses may result in improvement in Das-Naglieri scores.

Comparative Studies

While placebo-controlled studies are necessary to demonstrate the efficacy of new products, clinicians often rely on the results of comparison trials to guide decisions related to initiating and titrating ADHD medications. With the expansion in treatments options over the past 20 years, there has been a steady increase in the number of studies comparing two or more products. Several valuable studies have been published over the past year.

Long-acting Methylphenidate

In 2013, Coghill and colleagues performed a systematic review of studies comparing long-acting methylphenidate formulations that was published in 2013.⁵ The authors reviewed 34 studies, including not only randomized controlled trials, but also pharmacokinetic studies, clinical trials conducted in structured school-like study environments, and an observational study. The authors found no one product superior to the others. When reviewing the studies as a group, efficacy reflected the pharmacokinetics of the drug product. They

suggest that the choice of methylphenidate product correspond with the individual patient's needs, as the available products have significant differences not only in length of effect but also in onset and peak effect. They also recommend additional studies of the long-acting methylphenidate products to further evaluate the effects of comorbidities and symptom severity on treatment response.

Guanfacine-Atomoxetine

The efficacy of extended-release guanfacine and atomoxetine was recently evaluated using a new methodology termed matching-adjusted indirect comparison (MAIC).⁶ The tool uses patient data from a clinical trial of one treatment to compare to aggregate data from a second treatment. Studies included in the assessment had comparable study designs and patient characteristics. Using MAIC, the authors identified significantly greater reductions in the mean ADHD-RS-IV total scores from baseline to study completion with guanfacine compared to atomoxetine, with a relative improvement of -7.0 (standard error 2.2), $p < 0.01$. Differences in hyperactivity/impulsivity and inattention subscores were also significant, with relative improvement values of -3.8 (1.2) and -3.2 (1.3) respectively. Using MAIC methodology, guanfacine was found to produce greater improvement in ADHD symptoms than atomoxetine over a wide range of doses. The reductions in ADHD-RS-IV scores remained greater with guanfacine even when comparing low-dose therapy, 0.075-0.09 mg/kg/day, to a standard atomoxetine dose of 1.2 mg/kg/day (relative improvement -6.0 (2.7), $p < 0.05$), or when comparing standard doses of guanfacine to atomoxetine doses greater than 1.2 mg/kg/day (-7.6 (1.4), $p < 0.01$).

Methylphenidate-Atomoxetine

A comparison of OROS methylphenidate and atomoxetine was published in the June issue of *The Journal of Child Psychology and Psychiatry*.⁷ A total of 102 children with ADHD (mean age 10.5 ± 2.7 years) were enrolled into this randomized, double-blind cross-over study. Each medication was titrated over a 4-6 week period, with a 2-week placebo period between each treatment arm. Sustained attention was assessed by the Conners' Continuous Performance Test II (CPT-II) reaction time (RT), as well as reaction time variability (RTSD), and omission errors. Methylphenidate produced significantly greater improvement than atomoxetine on RT, RTSD, and errors ($p < 0.05$), indicating a more substantial effect on sustaining attention.

Atomoxetine-Lisdexamfetamine

Another comparison study was recently conducted with atomoxetine and lisdexamfetamine.⁸ This 9-week randomized, double-blind study enrolled 267 children between 6 and 17 years of age who had an inadequate response to methylphenidate. Patients received either lisdexamfetamine at a dose of 30, 50, or 70 mg once daily or atomoxetine at a dose of 0.5-1.2 mg/kg/day for patients less than 70 kg or 40, 80, or 100 mg/day for those weighing 70 kg or more. A significantly greater number of patients in the lisdexamfetamine group met the criteria for response, a reduction in ADHD-RS-IV total score of 25% or greater (91 versus 77%, $p < 0.01$). The percentage of patients with a reduction of more than 30% and the percentage with more than a 50% reduction were also significantly higher with lisdexamfetamine. Rates of sustained response in ADHD-RS-IV or CGI Improvement scores over the duration of the study were also higher in the patients given lisdexamfetamine. Adverse effects were similar in the two treatment arms. The authors concluded that lisdexamfetamine produced a more rapid and robust response than atomoxetine in patients who failed to respond to methylphenidate, suggesting that lisdexamfetamine may be a better option in this patient population.

Methods for Predicting or Assessing Response

While numerous studies have demonstrated improved school performance and behavior in social settings with treatment, several recent papers have focused on new methods of predicting or assessing the effects of ADHD treatment.

Cognitive Testing to Predict Response

A preliminary analysis of the International Study to Predict Optimized Treatment in ADHD has been recently published which identified a cognitive testing battery useful in predicting which patients will respond to methylphenidate.⁹ A group of 284 children and adolescents (6-17 years of age, mean age 11.9 ± 3.2 years) received methylphenidate for a period of 6 weeks. ADHD-RS-IV scores were assessed at baseline and the 6-week visit, with a reduction of 25% or greater considered a positive response. The overall response rate to methylphenidate in this patient sample was 62%.

All patients also underwent a cognitive test battery at baseline. Five tests were found to be significant discriminators of eventual methylphenidate response: accuracy on the switching of attention test, reaction time on the continuous performance test, time to complete

the executive maze run without error, reaction time on the verbal interference test, and the number of correct digit span trials. Testing identified three groups of patients less likely to respond to methylphenidate. Of the patients younger than 10 years of age who had poor planning implementation based on low maze scores, only 18% responded to methylphenidate. In patients 10 years and older who had low switching of attention scores and high scores on the verbal interference test, the response rate was only 44%, while in the patients with normal or high switching of attention accuracy, but very low sustained attention scores (continuous performance test scores less than the 5th percentile), only 40% responded to treatment with methylphenidate.

Two groups were identified who had higher response rates to methylphenidate. Of those 10 years and older who had low switching of attention and verbal interference scores, 85% responded to treatment. Patients with normal to above-normal continuous performance test scores and above average scores on the digit span tests had an 83% response rate. The authors suggest that simple cognitive tests performed at diagnosis may be a useful tool for predicting response to methylphenidate and minimizing the time to effective treatment.

Assessment of Cognitive Domains

In an article published recently in *Child Neuropsychology*, the Cambridge Neuropsychological Test Automated Battery (CANTAB) was used to provide an objective assessment of response to OROS methylphenidate.¹⁰ The authors evaluated a group of adolescents with ADHD prior to initiation of therapy and again at 1 year. Compared with their baseline values, there was significant improvement in spatial working memory, rapid visual processing, verbal recognition memory, set shifting, and inhibition/vigilance. When compared to a group of adolescents without ADHD, the ADHD patients had significant differences in several CANTAB tasks, but these differences were no longer present after 1 year of treatment. Assessment of CANTAB tasks may prove to be another useful tool in assessing response to ADHD treatment.

Effects on Driving Performance

Patients with ADHD are known to be prone to having impaired driving performance. Studies reporting higher rates of traffic violations and accidents in adults with ADHD date back to the 1970s. Treatment has been shown to improve driving performance, whether assessed on

driving courses or using driving simulators, but there is considerable variation in how these studies have been performed.

A systematic review of the more scientifically rigorous studies was recently published in *European Neuropsychopharmacology*.¹¹ The authors identified 15 randomized controlled trials evaluating the effects of methylphenidate, amphetamines, or atomoxetine. Across the studies evaluated, stimulants consistently improved driving performance. The use of OROS methylphenidate and immediate-release methylphenidate resulted in significantly better driving performance than placebo or in the controls given no treatment. The authors noted, however, that studies of immediate-release methylphenidate have shown worsening of performance with night driving and a potential rebound effect late at night with extended release methylphenidate preparations. Likewise, amphetamine salts have shown improvement in daytime driving performance but not in nighttime driving. Two placebo-controlled trials of lisdexamfetamine found a beneficial effect on daytime driving, but the studies with atomoxetine have shown mixed results.

Summary

The number of treatment options for children and adolescents with ADHD continue to increase, making choice of an agent difficult. There is now a growing body of literature aimed at assisting clinicians with these decisions, including head-to-head comparisons and descriptions of new methods of predicting and assessing response.

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Formulary Update

The Pharmacy and Therapeutics Committee did not meet in July. The results of their combined July/August meeting will be published in the August issue of the newsletter.

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