ADHD Treatment Across the Life Cycle

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Since attention-deficit/hyperactivity disorder (ADHD) is usually diagnosed in children, evidence from the studies of pharmacologic treatments for children with ADHD is used to inform pharmacologic treatment recommendations for adults. A large percentage of children diagnosed with ADHD have symptoms that persist into adolescence and adulthood. Evidence shows that pharmacologic treatments improve functional outcomes in children with ADHD, and studies using similar pharmacologic treatments show positive results in adults with ADHD. This article reviews the use of long-acting methylphenidate, mixed amphetamine salts, desipramine, monoamine oxidase inhibitors, bupropion, and atomoxetine in studies of children, adolescents, and adults with ADHD.

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Evidence from studies of pharmacologic treatments for children with attention-deficit/hyperactivity disorder (ADHD) is used to inform pharmacologic treatment recommendations for adults. Most controlled studies of medication in ADHD involve elementary-aged children, while research with other age groups—preschool-aged children, adolescents, and adults—is not extensive. Many studies of stimulant pharmacologic treatment have demonstrated improvement in the core symptoms of ADHD (inattentiveness, overactivity, and impulsivity), with other studies documenting improvement in the domains of self-esteem, cognition, and social and family function.

One of the most extensive studies for the treatment of ADHD symptoms is the Multimodal Treatment Study of Children With ADHD (MTA),[1] in which patients who were in the medication management group showed major improvement. The MTA was a 14-month clinical trial of 579 children with DSM-IV–diagnosed ADHD, combined type, who were randomly assigned to 1 of 4 treatment conditions—medication management, behavior management, combined medication management and behavior management, or community-based treatment. Fifty-six percent of the subjects in the medication management group improved as opposed to 36% of those in the community-based treatment group, according to teacher reports of hyperactive impulsive symptoms. The community-based treatment group received stimulant medications, generally methylphenidate, as did the medication management group; however, the medication management group had a mean of 2.9 daily doses, while the community-based treatment group had a mean of 2.1 daily doses. Medication management scores also exceeded behavior treatment scores but were similar to those of the combined treatment group, according to the parents' and teachers' ratings of inattention and the teachers' ratings of hyperactivity. These findings indicated that medication management should result in more appropriate behavior among children and adolescents. The MTA was one of few long-term ADHD studies, but the study conclusions are limited by lack of blinded treatment and lack of a placebo group. The community care group received similar types of medications as the medication management group, so it is difficult to conclude which of these treatment options may be more effective overall, although significant differences were seen among the groups. Nevertheless, evidence shows that pharmacologic treatments improve core symptoms and functional outcomes in children with ADHD.

STIMULANT TREATMENTS FOR CHILDREN

Pharmacologic stimulant treatments such as methylphenidate and mixed amphetamine salts improve core symptoms and functional outcomes in children with ADHD. Stimulants have been the most widely studied treatment for ADHD, and long-acting formulations of methylphenidate and mixed amphetamine salts have been shown to be robustly effective. Stimulants are well tolerated with a potential for (usually mild) adverse effects such as weight loss, stomachaches, headaches, initial

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insomnia, and irritability.[2] Researchers are investigating whether the long-acting formulations of stimulants are as effective in improving symptoms and decreasing adverse effects as the short-term versions.

Long-Acting Stimulants

Two recent studies[3,4] assessed the effectiveness of long-acting stimulants compared with placebo, their immediate-release counterpart, or both. Long-acting formulas were designed to relieve the child of taking medication at school and the school from dispensing medication.

Wolraich et al.[3] randomly assigned 282 patients with DSM-IV ADHD to 1 treatment per day with osmotic, controlled-release OROS methylphenidate (N = 95), 3 treatments per day with immediate-release methylphenidate (N = 97), or placebo (N = 90). The patients' diagnoses of ADHD were confirmed by a Diagnostic Interview Schedule for Children (version 4); the Swanson, Nolan, and Pelham, version IV Scale; and the Iowa Conners Rating Scale. The 2 study drugs improved symptoms of ADHD compared with placebo but did not show significant differences when compared with each other.

Biederman and colleagues[4] compared a single-dose, extended-release formula of mixed amphetamine salts (N = 374) with placebo (N = 210) in a 3-week, randomized, parallel-group study that assessed the effects of treatment on children aged 6 to 12 years and used a dose escalation regimen to show a dose-dependent response. All subjects started with a 1-week washout phase, and 374 were treated with 10 mg/day of mixed amphetamine salts for 1 week. During week 2, the dose was increased to 20 mg/day in 245 of the 374 patients. In week 3, the dose was increased to 30 mg/day in 124 of the previous 245 patients. Improvement was dose-dependent, significantly ($p < .001$) greater than placebo, and seen in all 3 weeks according to the teacher ratings of the Clinical Global Impressions scale (CGI), but a larger improvement was seen in the group that received 30 mg/day.

Even though stimulants are the most studied treatments for ADHD, some patients may not respond to treatment and others may not tolerate the adverse effects[2]; therefore, alternative treatments are needed.

NONSTIMULANT TREATMENTS FOR CHILDREN

Several nonstimulants, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), bupropion, and atomoxetine have been tried in children with ADHD. Atomoxetine, however, is the only nonstimulant ADHD medication approved by the U.S. Food and Drug Administration (FDA). Alternatives to stimulant treatment have varying degrees of effectiveness, and some have important restrictions and adverse effects, including a risk of cardiac effects with TCAs and strict dietary regulations with MAOIs.[2]

Tricyclic Antidepressants

My colleagues and I[5] studied the effects of the TCA desipramine on children (N = 24) and adolescents (N = 17) with DSM-IV ADHD and comorbid Tourette's disorder (N = 37) or DSM-IV ADHD and comorbid non-Tourette's chronic tic disorder (N = 4) in a 6-week, double-blind, placebo-controlled parallel trial. The doses of desipramine and placebo escalated each week. During week 1, patients were treated with a mean ± SD dose of 1.4 ± 0.2 mg/kg/day, and by the end of week 6, the dose had increased to 3.4 ± 0.3 mg/kg/day. The desipramine treatment group (N = 21) showed statistically significant ($p < .001$) response of ADHD symptoms compared with placebo by week 2 with a dose of 2.3 ± 0.4 mg/kg/day, and the group continued to improve throughout the 6 weeks. In addition, tic symptoms improved on medication. Adverse effects include decreased appetite, difficulty in sleeping, and headaches, as well as an increase in diastolic blood pressure and pulse.

Monoamine Oxidase Inhibitors

The use of MAOIs in children is severely limited due to hypertensive risks from dietary restrictions and drug-drug interactions. Zametkin et al.[6] used dextroamphetamine, clorgiline, and tranylcypromine in a small 12-week, double-blind crossover study for the treatment of DSM-III attention deficit disorder with hyperactivity in 14 boys. The patients went through a 2-week placebo washout phase and then entered the first 3-week treatment stage. All patients received 10 mg of dextroamphetamine in the morning and 5 mg of dextroamphetamine at noon, 6 received clorgiline twice a day given in 5-mg doses, and 8 received tranylcypromine twice a day given in 5-mg doses. In the second phase, tranylcypromine was used instead of clorgiline. After a second, 2-week placebo washout phase, the patients entered the second, 3-week treatment phase. Patients in all 3 treatment groups showed significant improvement; however, many precautions had to be taken to ensure safety—diets including school lunches were changed, blood pressure was monitored closely, and all previously taken stimulant medication was discarded.

Bupropion

Bupropion has been examined for ADHD treatment across the life span in a number of open and controlled studies. Conners et al.[7] conducted a multicenter, double-blind study that assessed the effects of bupropion (N = 72) compared with placebo (N = 37) in children aged 6 to 12 years with DSM-III ADHD. After a 1-week washout phase, patients were treated twice daily for 4 weeks. All 72 patients started with 3 mg/kg/day; their doses were increased according to weight up to a maximum of 6 mg/kg/day. The effects of treatment were assessed by the Conners Parent and Teacher Questionnaire, the CGI-Severity of Illness scale (CGI-S), and the Sternberg Short-

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Term Memory Task–Continuous Performance test. According to the Conners Teacher Questionnaire, the teachers noticed a significant response to treatment by the third day; however, the parents did not notice improvement until the fourth week, possibly due to a large placebo effect. Clinician ratings in this trial varied widely with some sites documenting improvement and other sites not. While generally well tolerated, the medication caused statistically significant adverse effects including nausea, vomiting, and rash.

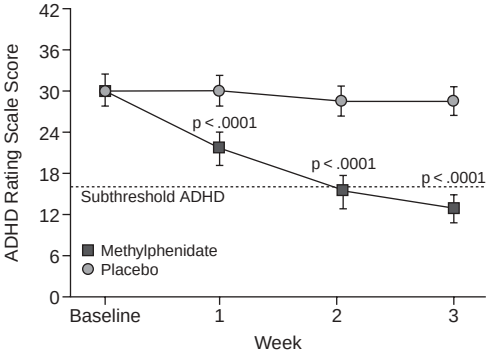
Atomoxetine

Atomoxetine is the latest ADHD treatment to receive FDA approval. Two identical 12-week, stratified, randomized, double-blind, placebo-controlled trials reported by Spencer et al.[8] were conducted in children who met DSM-IV criteria for ADHD. The patients receiving atomoxetine could receive 2.0 mg/kg/day for a maximum total of 90 mg/day, while the patients receiving methylphenidate could receive up to 1.5 mg/kg/day or a maximum total of 60 mg/day. The primary efficacy outcome measure was the mean change from baseline to endpoint in the ADHD Rating Scale total score. Secondary efficacy measures included the CGI-ADHD-Severity scale and the Conners Parent Rating Scale-Revised, Short Form. Patients treated with atomoxetine showed statistically significant improvements over those treated with placebo on all 3 measurements. On the ADHD Rating Scale, the 2 studies showed similar results; patients treated with atomoxetine showed a mean decrease of 15.6 in one study and 14.4 in the other, while patients treated with placebo showed a mean decrease of 5.5 and 5.9, respectively. On the CGI-ADHD-Severity scale, results were also similar; patients treated with atomoxetine showed a mean decrease of 1.2 in one study and 1.5 in the other, but patients treated with placebo showed a mean decrease of 0.5 and 0.7, respectively.

Michelson et al.[9] studied the efficacy of atomoxetine at 3 different doses in children and adolescents diagnosed with DSM-IV ADHD. Patients (N = 297) were randomly assigned to receive atomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day, or 1.8 mg/kg/day or placebo for approximately 8 weeks. All patients receiving atomoxetine started at 0.5 mg/kg/day, and doses were titrated weekly in 84 patients to 1.2 mg/kg/day and in 85 patients to 1.8 mg/kg/day. The 2 groups receiving higher doses showed improvement compared with placebo. The higher doses were well tolerated, and there was no statistical difference in the frequency of the adverse effects between dosage groups. The 2 clinically significant adverse effects were somnolence and anorexia.

In the Michelson et al.[9] trial, quality-of-life measurements were assessed. The improvement of ADHD symptoms and functional outcomes were dose-dependent. As the dose of atomoxetine increased, the patient's symptoms decreased, while the patient's functional outcomes, i.e., the patient's self-esteem and psychosocial capacity to learn, behave, and socialize appropriately increased. The improved functional outcomes were also reflected in a decreased level of stress among the parents from worrying about their affected child and decreased amount of time the parents spent taking care of their child.

Figure 1. ADHD Rating Scale Scores With Methylphenidate Versus Placebo in Adult ADHD[a]



[a]Reprinted with permission from Spencer et al.[10]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

STIMULANT TREATMENTS FOR ADULTS

Treating adults for ADHD is a new area of research, and relatively few controlled studies have been conducted. However, when the results of the controlled studies that have been completed in adults are compared with those in children and adolescents, the results are similar. More research is needed, because many children affected by ADHD have symptoms that continue into adulthood.

My colleagues and I[10] conducted a randomized, placebo-controlled, crossover study that assessed dosing of methylphenidate in 25 adults aged 18 to 60 years who were diagnosed with DSM-III-R childhood-onset or current ADHD. The patients started with placebo or 0.51 ± 0.01 mg/kg/day of methylphenidate and were titrated to the target dose of 1 mg/kg/day of methylphenidate. Methylphenidate treatment was more effective than placebo and response was increasingly robust with increases in daily doses (Figure 1). Symptom improvement appeared to be dose-dependent, and methylphenidate proved significantly more effective than placebo (response rate of 78% vs. 4%, $p < .0001$) as assessed by the ADHD Rating Scale. Methylphenidate was well tolerated. Two patients withdrew from the study early on, and all but 3 of the remaining 23 patients tolerated the full dose. The most common adverse effects were loss of appetite (26%), insomnia (22%), and anxiety (22%). More research is needed on the long-term efficacy of methylphenidate and quality-of-life measurements for adults.

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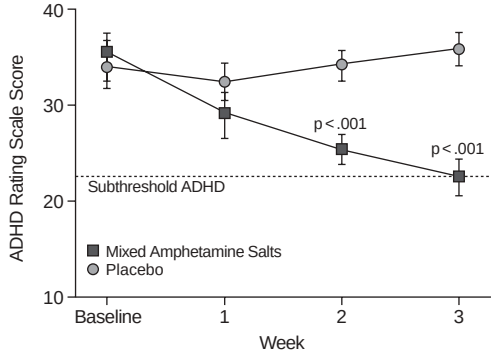
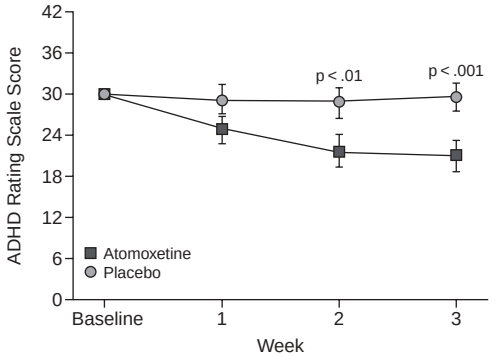
Figure 2. Mixed Amphetamine Salts Versus Placebo for ADHD in Adults[a]



[a]Reprinted with permission from Spencer et al.[11]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 3. ADHD Rating Scale Scores With Atomoxetine Versus Placebo in Adult ADHD[a]



[a]Reprinted with permission from Spencer et al.[15]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Another stimulant treatment for ADHD in adults is mixed amphetamine salts. We performed a 7-week, randomized, double-blind, placebo-controlled crossover study of 27 adults with DSM-IV childhood-onset ADHD assessing the use of mixed amphetamine salts compound.[11] The mixed amphetamine salts treatment showed a significant ($p < .001$) reduction of symptoms compared with placebo on the ADHD Rating Scale, with reduction seen in the first 4 weeks of treatment (Figure 2). According to the CGI, 66.7% of patients receiving mixed amphetamine salts improved, while only 3.7% of patients receiving placebo were rated as improved. Anxiety levels were not affected, and the adverse effects—appetite suppression, agitation, and a slight increase in blood pressure—were minimal as compared with placebo. Appetite suppression may be a positive result for some adults, and no one discontinued treatment because of the adverse effects.

NONSTIMULANT TREATMENTS FOR ADULTS

The nonstimulants desipramine and bupropion have been studied in adults with ADHD. Atomoxetine has recently been approved by the FDA for the treatment of ADHD in adults.

Tricyclic Antidepressants

Wilens et al.[12] studied the effects of desipramine on adults with DSM-III-R ADHD in 43 patients. The mean dose was 171.1 mg/day at week 2, 161.1 mg/day at week 4, and 147.4 mg/day at week 6. Nine patients reached the target dose of 200 mg/day of desipramine. Ten patients receiving desipramine had their dose lowered because of adverse effects. In the group treated with desipramine, 68% of subjects improved as assessed by the CGI, and desipramine proved significantly ($p < .0001$) more effective than placebo.

Bupropion

Wilens and colleagues[13] performed a 6-week, double-blind, placebo-controlled, randomized, parallel trial of sustained-release bupropion at a dose of up to 200 mg/day divided into 2 daily doses. The patients started with 100 mg/day, and their dose was increased weekly by 100 mg/day unless adverse effects were noticed. Forty patients who met DSM-IV ADHD criteria enrolled in this study, and 38 completed it. Bupropion treatment showed a significant ($p < .05$) decrease in scores on the ADHD symptom checklist; the patients treated with bupropion showed a 42% reduction, compared with a 24% reduction in the group treated with placebo. Five patients had their doses lowered because of adverse effects. Wender and Reimherr,[14] in an open trial of bupropion, documented improvement of ADHD symptoms over a 1-year period.

Atomoxetine

Atomoxetine is the only medication approved by the FDA for ADHD in adults. In 1998, we conducted a double-blind, placebo-controlled, crossover pilot study of atomoxetine, which was known at the time as tomoxetine, in 22 adults with DSM-III-R childhood-onset ADHD.[15] During the first 3-week treatment phase, patients received 40 mg/day of atomoxetine in week 1 and 80 mg/day divided in 2 daily doses for weeks 2 and 3. A 1-week placebo washout period followed the first treatment phase. Eleven patients treated with atomoxetine and 2 placebo-treated patients showed improvement. At week 3, the mean decrease in ADHD Rating Scale scores was significantly ($p < .001$) greater in atomoxetine-treated patients compared with placebo-treated patients (Figure 3). Atomoxetine was generally well tolerated with few mild side effects including appetite suppression and insomnia. Only 1 patient dropped out of the study because of emergent anxiety.

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Two identical, randomized, double-blind, placebo-controlled trials[16] at 17 and 14 outpatient sites also investigated the effects of atomoxetine on ADHD in adults. Patients with current major depression, anxiety disorder, current or past bipolar or psychotic disorders, serious medical illness, alcohol dependence, and drug use at the time of the study were excluded. Subjects underwent a 1-week washout and evaluation and then a 2-week placebo lead-in phase. The patients who still met the ADHD criteria after the first 3 weeks were then randomly assigned to treatment for 10 weeks. Patients were randomly assigned to atomoxetine (study 1, N = 141; study 2, N = 129) or placebo (study 1, N = 139; study 2, N = 127). Patients in the atomoxetine group were started on 60 mg/day divided into 2 daily doses, and, if necessary, the dose was increased to 120 mg/day after week 4. Both groups treated with atomoxetine showed improvement compared with the groups treated with placebo as assessed by the inattentive and hyperactivity/impulsivity subscales of the Conners Adult ADHD Rating Scale: Investigator (CAARS:Inv).

Following this 10-week study, 384 of the patients elected to enter an open-label extension study for approximately 34 weeks.[17] Following a 4-week discontinuation phase, patients were openly treated with 60 to 120 mg/day of atomoxetine. The results were assessed by the CAARS:Inv, and the total ADHD symptom scores decreased by 43.5%. In two thirds of the patients, CAARS scores improved by at least 30%. CGI scores in 80% of patients decreased by 1 point, and in 47%, by 2 points. The discontinuation rate from adverse effects was 7.8%.

CONCLUSION

Many medications have been tested for the treatment of ADHD, and it has been shown that most pharmacologic treatments used for ADHD in children are also effective in adults. Currently available treatments have the common mechanism of affecting the catecholaminergic (dopamine, norepinephrine) system. The stimulants and mixed amphetamine salts and the nonstimulants desipramine, bupropion, and atomoxetine have been tested for ADHD in adults, and atomoxetine recently received FDA approval for adult ADHD.

Drug names: mixed dextroamphetamine and amphetamine (Adderall XR), atomoxetine (Strattera), bupropion (Wellbutrin SR and others), desipramine (Norpramin and others), methylphenidate (Metadate-CD, Concerta, and others), tranylcypromine (Parnate).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, mixed dextroamphetamine and amphetamine and methylphenidate are not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults; and bupropion, desipramine, and tranylcypromine are not approved for the treatment of ADHD.

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