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# Emerging Studies in Pediatric ADHD Pharmacotherapy

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**A review of the latest published and emerging study data on  
the pharmacotherapeutic options for the treatment of pediatric ADHD**



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September 2006

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# Emerging Studies in Pediatric ADHD

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The University of Cincinnati College of Medicine designates this activity for a maximum of 1 *AMA PRA Category 1 Credit*<sup>™</sup>. Physicians should only claim credit commensurate with the extent of their participation in the activity.

## TARGET AUDIENCE

This activity is designed for pediatricians and child/adolescent psychiatrists.

## STATEMENT OF NEED

The pharmacotherapeutic options for the treatment of pediatric attention-deficit/hyperactivity disorder (ADHD) continue to expand, increasing the amount of data available for both approved and novel treatment options. In order for clinicians to make informed choices regarding treatment, it is necessary to educate clinicians on the latest information on the safety and efficacy of the pharmacotherapeutic options available for pediatric ADHD patients.

## LEARNING OBJECTIVES

After completing this activity, participants should be able to:

- Outline the clinical and economic burden of ADHD
- Describe the latest data on the efficacy of stimulant and nonstimulant treatment options for pediatric ADHD
- Summarize the recent data on the adverse events and safety profiles of the pharmacotherapeutic treatment options for pediatric ADHD

Release Date: September 25, 2006; Expiration Date: September 25, 2007

There is no fee associated with this activity.

## INDEPENDENT CLINICAL REVIEWER

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## DISCLOSURE INFORMATION

In accordance with the disclosure policies of the University of Cincinnati College of Medicine and Princeton Media Associates, the effort is made to ensure balance, independence, objectivity, and scientific rigor in all educational activities. These policies include resolving all conflicts of interest between faculty and commercial interests that might otherwise compromise the goal and educational integrity of this activity. All faculty members participating in this activity have disclosed all relevant financial relationships with commercial interests. The planners of this activity have reviewed these disclosures and have determined that the faculty relationships are not inappropriate in the context of their respective presentations and are not inconsistent with the educational goals and integrity of the activity.

The faculty reported the following:

**Dr. Stein:** Grant support—Eli Lilly and Company

Planning Committee Kay Weigand, University of Cincinnati College of Medicine, Office of Continuing Education, and Kristin Dickie, Rosemary Hodgson, Rich Keenan, Anastasia Perkowski, and Donna Coffman, MD, Princeton Media Associates, have disclosed they have no relevant financial relationships with any commercial interests.

The University of Cincinnati College of Medicine and Princeton Media Associates require faculty to inform participants whenever off-label/unapproved uses of drugs or devices are discussed in their presentation.

The following off-label/unapproved drugs or devices are discussed: lisdexamfetamine dimesylate and modafinil in the treatment of pediatric ADHD.

## GRANT SUPPORT

This activity is supported through an unrestricted educational grant from Shire Pharmaceuticals Inc.

To be eligible for documentation of credit, participants must read all monograph content (print or online), log on to [www.princetoncme.com](http://www.princetoncme.com) to complete the 10-question post-test with a score of 70% or better, and complete the online evaluation form. **Participants who successfully complete the post-test and evaluation form online may immediately print their documentation of credit.** Please e-mail [info@princetoncme.com](mailto:info@princetoncme.com) or call 609-371-1137 if you have questions or need additional information.

# Emerging Studies in Pediatric ADHD Pharmacotherapy

Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurobehavioral disorder that leads to functional impairment with pervasive inattention, hyperactivity, and impulsivity.<sup>1</sup> Symptoms develop before the age of 7 years, although in many, the disorder is present for years before the diagnosis is made.<sup>2</sup>

It is estimated that 7.8% of school-age American children have been diagnosed with ADHD.<sup>1</sup> To establish a diagnosis of ADHD, symptoms must be persistent and cause impairment in at least 2 settings, such as home, school, or work.<sup>2</sup> Children with ADHD may have careless and disorganized schoolwork and difficulty sustaining attention through tasks and play activity. In social situations, children with ADHD frequently shift the conversation, do not listen, or have difficulty concentrating on the conversation. Hyperactivity manifests as fidgeting, squirming, or not remaining seated when it is expected; running and climbing when it is inappropriate; having difficulty engaging in quiet activity; and talking excessively. Impulsivity presents as impatience, blurting out answers before the question has been finished, difficulty waiting for one's turn, interrupting others, frequent occurrence of accidents, and participation in dangerous activities without considering the consequences. By late childhood or early adolescence, excessive motor activity may be confined to fidgetiness or feeling restless, and impulsivity may lead to breaking familial, interpersonal, and educational rules; however, inattentive symptoms persist through adolescence.<sup>2</sup>

This *First Report*<sup>®</sup> examines the burden of ADHD and reviews data from studies published and presented in 2006 on the efficacy and safety of both approved and novel pharmacotherapeutic options for the treatment of children with ADHD.

## THE BURDEN OF ADHD

In the United States, ADHD-related treatment costs for children are estimated to total \$1.59 billion, with total excess overall healthcare costs estimated at \$2.8 billion.<sup>3</sup> Children with ADHD have higher direct medical costs than non-ADHD matched controls (difference range, \$503-\$1343).<sup>3</sup>

Nonpsychiatric medical problems that contribute to increased medical costs in children with ADHD include learning disabilities and recurrent accidents (eg, automobile accidents in adolescents). Children with ADHD are more likely to have an accident claim filed on insurance, with rates of 28% versus 18% of non-ADHD children. In adolescents with ADHD, 32% were reported to have accident claims versus 23% of non-ADHD peers.<sup>3</sup>

The costs related to ADHD are not confined to direct and indirect medical costs of treatment of ADHD. There are also costs related to the social consequences of the illness, which are more difficult to quantify. Some studies have attempted to assess costs related to the increased rates of social dysfunction, criminality, and comorbid diagnoses, such as learning disabilities, anxiety disorder, and behavioral problems. A study by Matza et al determined that children with ADHD have higher juvenile arrest rates compared to normal subjects (range, 39%-46% vs 11%-20%, respectively) and higher total criminal costs (costs incurred by victims and costs to the criminal justice system) of \$12,868 versus \$498 for normal subjects.<sup>3</sup> The presence of comorbid conditions

increases the medical care costs for these children as well. For example, depression increases costs by an average of \$358 per patient per year and anxiety increases costs an average of \$499 per year.<sup>3</sup>

In addition to economic costs, ADHD takes a toll on the quality of life of these children and their families.<sup>3</sup> For the child, ADHD can mean poor academic performance, poor peer relationships, and problematic relationships with family members. ADHD in children is frequently linked to strain in the parent-child relationship, disturbed marital functioning in the parents, and high parental stress.<sup>3</sup> Children with ADHD are also frequently rejected by their peers, possibly due to disruptive and aggressive behavior. Studies suggest that these children are less likely to reach the level of educational and occupational achievement seen in their peers.<sup>3</sup>

## THE IMPACT OF PHARMACOTHERAPY

In 2003, approximately 2.5 million children ages 4 to 17 years with ADHD were taking prescription medication for their ADHD symptoms, representing approximately 56% of all children with ADHD.<sup>1</sup> Although stimulant medications are considered effective first-line therapy for ADHD, concern about possible adverse effects and long-term effects on the health of children treated with stimulants remains. As a result, studies continue to examine the efficacy and associated adverse effects of ADHD pharmacotherapy.<sup>1</sup>

Recent data confirm the benefits of treatment with stimulant medication in reducing the symptoms of ADHD. In a study designed to determine if children with ADHD treated with stimulants demonstrated improved functioning, 18 boys were divided into study groups based on treatment history.<sup>4</sup> One group had previous treatment with stimulants, another group had not had previous treatment for ADHD, and the last group was a normal control group. None of the children with ADHD had a comorbid diagnosis, and behavior measures were performed with the Behavior Assessment System for Children completed by parents. The untreated children with ADHD scored poorer than either the treated ADHD group or the control group.<sup>4</sup> Symptoms of anxiety, somatization, atypical behavior, withdrawal, and depression were elevated for both ADHD groups compared to the control group, but the untreated ADHD group had the poorest scores on measures of these symptoms.<sup>4</sup> The study concluded that while both ADHD groups demonstrated internalizing behaviors, the untreated group had more difficulties in both the internalizing and externalizing behaviors.<sup>4</sup> Studies of atomoxetine (selective norepinephrine reuptake inhibitor), the only nonstimulant approved for use in the treatment of ADHD, indicate that this agent similarly reduces the symptoms of ADHD, leading to an equally efficacious benefit of treatment.<sup>5-8</sup>

## REVIEW OF STIMULANT TREATMENT

There are several recently published studies, as well as emerging data being presented, evaluating the efficacy and safety of stimulant medications. These studies have focused on newer methods and formulations of medication delivery, such as the methylphenidate transdermal system (MTS), as well as extended-release formulations of dexamethylphenidate (d-MPH), methylphenidate (MPH), and mixed amphetamine salts (MAS).

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*Recent Published Data on Stimulant Medication.* MTS is a nonoral delivery system for MPH composed of a diffusion-based patch combined with a multipolymeric adhesive patch to provide reproducible blood levels of MPH.<sup>9</sup> To determine efficacy, duration of action, and tolerability of this system, MTS was studied in a randomized, double-blind, placebo-controlled, laboratory classroom assessment study in 80 participants.<sup>10</sup> Dosing was optimized over 5 weeks, after which the subjects were randomized

to 1 week of MTS or placebo followed by 1 week of the opposite treatment. The study noted improvements in all efficacy measures in the treatment groups, including ratings of attention, behavior, and academic performance. These benefits persisted through 12 hours, and there were no reported serious adverse events.<sup>10</sup>

D-MPH extended-release (ER) was compared to placebo in a randomized, double-blind, placebo-controlled, crossover study of 54 children with ADHD age 6 to 12 years to determine efficacy and safety.<sup>11</sup> Measures of predose and postdose symptoms were performed over 12 hours. The children treated with d-MPH-ER had significant improvements in classroom attention, deportment, and performance scores compared to children who were treated with placebo ( $P<.001$ - $P<.046$  over the 12-hour period).<sup>11</sup> There were no severe adverse events reported during the study.<sup>11</sup>

Osmotic release oral system (OROS)-MPH is a once-daily, controlled-release formulation. An 8-week, multicenter, open-label, randomized study designed to determine the tolerability and efficacy of OROS-MPH compared to immediate-release (IR)-MPH, randomized 147 subjects age 6 to 12 years with ADHD to receive either OROS-MPH or IR-MPH.<sup>12</sup> The doses were titrated to a clinically effective dose over a period of 4 weeks before the start of the 4-week study period. OROS-MPH showed statistically significant greater improvement in ADHD symptoms compared to IR-MPH in both the remission ( $P=.0002$ ) and the severity ( $P=.004$ ) measures. Both formulations were well tolerated and had similar adverse effects.<sup>12</sup>

In a study of the efficacy and safety of MAS-extended-release (XR), a 4-week, randomized, multicenter, double-blind, placebo-controlled, parallel-group, forced-dose titration study was conducted on 258 adolescents age 13 to 17 years who had ADHD.<sup>13</sup> There were statistically significant improvements in ADHD symptoms in all 4 treatment groups compared to placebo ( $P<.001$ ). Most adverse events were mild or moderate and none were serious.<sup>13</sup>

*Emerging Data on Stimulant Medication.* Emerging data also support the efficacy and safety of treating children with ADHD with stimulant medication.

The efficacy of MTS was compared to a placebo patch in a randomized, double-blind, multicenter, placebo-controlled, open-label, laboratory classroom, crossover study of 80 children with ADHD age 6 to 12 years. The Swanson, Kotkin, Agler, M-Flynn, and Pelham Department Rating Scale (SKAMP) scores for deportment, attention, and total ADHD symptoms were lower for patients treated with MTS than those treated with placebo.<sup>14</sup> Additional data presented looking at parent ratings of symptoms using the Conners' Parent Rating Scale-Revised also noted improvement with treatment compared to placebo.<sup>15</sup> The majority of adverse events were of mild or moderate intensity with 1 severe adverse effect (mood alteration) and no serious long-term adverse events.<sup>14,15</sup>

Lopez et al examined skin response and discomfort with the transdermal system using data from a randomized, double-blind, double-dummy, multicenter, parallel-group, placebo-controlled, dose-optimization study of MTS in 282 children with ADHD age 6 to 12 years.<sup>16</sup> Of those who completed the study, 6.1% reported no irritation, 11.2% reported minimal erythema, and 48% reported definite erythema. In the discomfort measures, study investigators reported that most patients had either no discomfort or only mild discomfort (mostly itching). After 9 hours of wear time, more than 75% of patients reported the patch to be completely or mostly adhered.<sup>16</sup>

A prospective, open-label, multicenter study of 171 children with ADHD age 6 to 12 years examined the effects of an abrupt conversion from oral MPH to a transdermal patch.<sup>17</sup> Safety, efficacy, and tolerability measures were rated using the ADHD Rating Scale-IV (ADHD-RS-IV), Clinical Global Impression-Severity (CGI-S), and Clinical Global Impression-Improvement (CGI-I). At baseline, CGI-S scores ranged from normal (17.1%) to markedly ill (0.6%), with the majority of patients being rated as mildly ill (42.7%). CGI-I scores at study end point ranged from very much improved (29.4%) to much worse (3.1%), with 43.6% of patients either minimally or much improved.<sup>17</sup> Changing from oral MPH to MTS resulted in a minimal initial worsening in symptoms compared to baseline. At the end point, ADHD-RS-IV scores were significantly better compared to baseline ( $P<.0001$ ).<sup>17</sup>

A pooled analysis of 2 randomized, multicenter, double-blind, crossover studies comparing d-MPH-ER to placebo in children age 6 to 12 years with ADHD in a laboratory classroom was performed to determine if there were differences in the treatment efficacy in children of different racial and ethnic backgrounds.<sup>18</sup> The children were grouped as white, black, or Hispanic/other, and SKAMP efficacy scores were analyzed. The improvements with d-MPH-ER over placebo were generally similar for all 3 groups, although there were some differences in response patterns. There was a borderline statistically significant greater improvement in scores in white patients than black patients ( $P=.0575$ ), and a nonsignificant greater worsening of scores in Hispanic/other children on placebo compared to the other groups. These results suggest that there are some racial/ethnic differences in ADHD symptoms, however, with treatment there are improvements in symptoms regardless of race/ethnicity.<sup>18</sup>

To measure improvement differences between boys and girls treated with OROS-MPH, data on 850 children were analyzed from a previous prospective, open-label, 3-week, randomized trial of treatment with OROS-MPH or atomoxetine.<sup>19</sup> In this analysis, only data on the

OROS-MPH group were reviewed. In the analysis, it was determined that baseline symptoms were similar between the boys and girls, and ADHD symptom improvement was comparable between the boys and girls treated with OROS-MPH at the end of the study.<sup>19</sup>

Two randomized, double-blind, placebo-controlled, parallel-group studies of children with ADHD age 6 to 12 years were designed to determine effectiveness of MTS compared to OROS-MPH in a naturalistic setting with clinician-based assessments. In both studies, MTS and OROS-MPH demonstrated similar efficacy and safety profiles.<sup>20,21</sup>

One 4-week, randomized, placebo-controlled, double-blind, parallel-group trial and 2 post-hoc analyses of another randomized study of MAS-XR examined rates of adverse events compared to placebo, and found that while rates of adverse events were higher in the MAS-XR groups, rates of adverse events decreased over time, and the agent was found to be well tolerated.<sup>22-24</sup>

In the 4-week trial of 258 adolescents age 13 to 17 years, rates of adverse events in week 1 with the MAS-XR treatment group were: emotional lability 2.3%, insomnia 7%, nervousness 3.9%, abdominal pain 4.3%, and anorexia 22.1%.<sup>22</sup> The rates of these adverse events decreased over the 4 weeks of treatment to rates of 0% for emotional lability, and 1.7% each for insomnia, nervousness, abdominal pain, and anorexia.<sup>22</sup> Headache rates were similar between the treatment groups and also decreased over time. Over the entire length of the study, weight loss was noted in 10.1% of subjects treated with MAS-XR and none of the placebo group. Of the total, 3.1% of patients discontinued treatment due to adverse events.<sup>22</sup>

The 2 post-hoc analyses of a 3-week, randomized, double-blind, parallel-group trial of treatment of children age 6 to 12 years with ADHD were conducted to examine tolerability and adverse events with MAS-XR. In the first analysis, designed to determine the tolerability of treatment in girls, the data demonstrated that most adverse events associated with MAS-XR were of mild or moderate intensity.<sup>23</sup> A total of 4 patients discontinued the study due to adverse events (1 placebo, 3 treatment).<sup>23</sup> In the second post-hoc analysis, the data for 584 subjects were reviewed to determine rates of adverse effects. In the MAS-XR group, 2.4% of the patients withdrew from the study due to adverse events.<sup>24</sup>

## REVIEW OF NONSTIMULANT TREATMENT

*Recent Published Data on Nonstimulant Medication.* Data indicate that while psychostimulants have well-established efficacy and safety profiles, nonstimulants may offer an alternative treatment option.<sup>5</sup> In a study designed to evaluate all published clinical studies, as of December 2005, comparing atomoxetine with psychostimulants (regardless of study design), all relevant efficacy and safety data were reviewed.<sup>5</sup> In the 5 trials found, patients on atomoxetine or psychostimulants had improvement in symptom scores.<sup>5</sup> No significant differences were reported between atomoxetine and IR-MPH formulations, and greater improvements were found in subjects treated with MAS-XR or OROS-MPH.<sup>5</sup>

Similar results were found in a study published in 2006 of girls treated with atomoxetine versus MAS-XR.<sup>6</sup> A post-hoc analysis of an 18-day, randomized, double-blind, parallel-group, forced-dose titration, laboratory school study of children treated with MAS-XR or atomoxe-

tine was done to determine the efficacy, time course of the effect, and tolerability in 57 girls age 6 to 12 years who have ADHD.<sup>6</sup> The groups had similar SKAMP department and attention scores at baseline, and these scores improved with treatment. Girls who were treated with MAS-XR had significantly greater improvement compared to atomoxetine ( $P<.001$ ). Efficacy was assessed from 2 to 12 hours; at 12 hours efficacy was demonstrated for MAS-XR, but not for atomoxetine. At the end of the 18-day study, both groups had a significant increase from baseline in mean number of math problems attempted and correctly answered ( $P<.001$ ).<sup>6</sup> Adverse effects for MAS-XR included decreased appetite, upper abdominal pain, insomnia, and headache. Adverse effects for atomoxetine included somnolence, upper abdominal pain, vomiting, nausea, and decreased appetite. MAS-XR demonstrated greater efficacy in SKAMP department and attention scores ( $P<.001$  for both).<sup>6</sup>

*Emerging Data on Nonstimulant Medication.* A randomized, double-blind, placebo-controlled study of 189 subjects age 8 to 18 years with ADHD was created to determine the efficacy of atomoxetine based on dosing levels using the ADHD-RS-IV rating scale and Bayesian clearance estimates.<sup>7</sup> Improvements in the scores were seen with each corresponding increase in the dosing of atomoxetine. At the maximum offered dose of 1.8 mg/kg/day, 86% of projected maximum improvement was reached in the hyperactivity/impulsivity scores compared to 62% at the minimum offered dose of 0.5 mg/kg/day. In the attention scores, 85% of projected maximum improvement was reached in children on the maximum dose compared to 64% of those on the minimum offered dose.<sup>7</sup>

A 4-week, open-label, titration pilot study of atomoxetine in 3- to 5-year-old children with ADHD (N=8) was designed to determine efficacy and safety at the best dose as determined with stepwise titration based on therapeutic response and tolerability.<sup>8</sup> There were improvements in symptom scores for hyperactivity/impulsivity, inattention, and global scores. Adverse events were mild to moderate and included stomach upset (3/8 children), reduced appetite (2/8), crying/irritability (2/8), feeling sleepy/tired (2/8), difficulty sleeping (1/8), and increased thirst (1/8).<sup>8</sup>

## REVIEW OF NOVEL PHARMACOTHERAPIES

Novel treatments for ADHD include lisdexamfetamine dimesylate (LDX), which is not currently FDA-approved, and modafinil, which is FDA-approved for the treatment of daytime drowsiness in patients with sleep disorders, but not for ADHD. Based on safety concerns, the supplemental new drug application for a proprietary dosage form of modafinil for use in ADHD was denied by the FDA on August 9, 2006. The manufacturer of the agent also announced its decision to stop pursuing development and approval of the agent for the treatment of ADHD.<sup>25</sup>

LDX is a prodrug of d-amphetamine that is not active until it is metabo-

Research continues  
into determining ways  
to improve the quality  
of life of children  
with ADHD.

lized, which results in a gradual release of the active metabolite, and it is this chemical makeup that suggests a reduced potential for abuse, drug diversion, and overdose toxicity, according to background information provided by study authors.<sup>26,27</sup> A phase 3, randomized, multicenter, double-blind, parallel-group study compared LDX to placebo in 230 children age 6 to 12 years with ADHD to determine the safety and efficacy of LDX.<sup>26</sup> The primary outcome measures were scores on the ADHD-RS-IV and safety measures (adverse events, vital signs, laboratory tests, electrocardiograms). Significant improvements in ADHD symptoms were noted at all doses of LDX compared to placebo ( $P < .0001$ ). Of the adverse events reported (including decreased appetite, insomnia, headache, and upper abdominal pain), 95% were mild to moderate. The majority of adverse events were noted in the first week of treatment, and decreased over the 4 weeks of the study.<sup>26</sup>

To compare the efficacy and safety of LDX to MAS-XR, a randomized, double-blind, 3-week, 3-way, crossover study randomized 52 children age 6 to 12 years with ADHD to the optimal dose of MAS-XR, the optimal dose of LDX (based on the optimal dose-equivalent of MAS-XR), or placebo.<sup>27</sup> Optimal doses of MAS-XR were determined by titration over a 3-week period. Both LDX and MAS-XR demonstrated similar results in the control of ADHD symptoms and behavior as measured by SKAMP score improvement, and both demonstrated statistically significant superiority over placebo ( $P < .0001$ ). There were no serious adverse events reported, and most adverse effects were mild to moderate. LDX treatment resulted in a 5-mm Hg diastolic blood pressure elevation compared to a 3-mm Hg increase in the MAS-XR-treated group. At 2.5 hours after dosing, the heart rate was 7 beats/minute higher and 5 beats/minute higher for LDX and MAS-XR, respectively, than the placebo group. The study concluded that LDX demonstrated comparable efficacy to MAS-XR and a similar adverse-effect profile.<sup>27</sup>

To determine safety and efficacy of treatment with modafinil in children age 7 to 17 years with ADHD, a 9-week, double-blind, randomized, flexible-dose study compared modafinil to placebo.<sup>28</sup> In the 200 children studied, modafinil demonstrated significant improvement in

ADHD symptoms at school and home compared to placebo ( $P < .0001$ ). Adverse effects occurred more frequently with modafinil than placebo and included insomnia, headache, decreased appetite, and weight loss, but discontinuation rates in the 2 groups were not statistically different.<sup>28</sup>

In a published literature review of the use of modafinil, it was found that 3 large studies demonstrated consistent ADHD symptom improvement compared to placebo, with mean reduction in symptoms on the ADHD-RS-IV of 15 to 19.7 points with treatment compared to a reduction of 7.3 to 10.1 points with placebo. Adverse events that were most commonly reported included insomnia, headache, and decreased appetite.<sup>29</sup>

The safety and efficacy of the modafinil film-coated tablets and the effects of abrupt cessation of treatment were assessed in children and adolescents in a randomized, double-blind, placebo-controlled, fixed-dose study.<sup>30</sup> Patients age 6 to 17 years with ADHD were treated with either modafinil or placebo. The ADHD-RS-IV and CGI-I scales were used to measure symptom response. Modafinil treatment resulted in improvement in ADHD symptoms compared to placebo, with significantly higher proportions of modafinil-treated patients receiving ratings of much improved or very much improved in CGI-I scales at all visits compared to placebo ( $P < .001$ ).<sup>30</sup> Half of the modafinil-treated subjects were abruptly changed to placebo after 5 weeks and were observed for adverse events for 2 weeks. No withdrawal symptoms occurred when modafinil was abruptly discontinued.<sup>30</sup>

## CONCLUSION

The symptoms of ADHD cause significant social, academic, and work impairment in affected children, and treatment has been shown to reduce the impairment. Treatment with stimulant and alternative medications has proven effective and safe, and research continues into determining ways to improve the quality of life and academic and work performance of these children so that they can function on levels similar to their peers in home, school, and work settings. ■

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