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**First
REPORT[®]**

Pharmacologic Management of Adult ADHD: Exploring the Balance of Treatment Efficacy and Adverse Events

**A review of the latest published and emerging study data on
the impact of adult ADHD on quality of life and on the
available pharmacotherapeutic options for
the treatment of adult ADHD**



Jointly sponsored by the University of Cincinnati College of Medicine and Princeton Media Associates

October 2006

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Pharmacologic Management of Adult ADHD

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This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the University of Cincinnati College of Medicine and Princeton Media Associates. The University of Cincinnati College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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

TARGET AUDIENCE

This activity is designed for primary care physicians and psychiatrists.

STATEMENT OF NEED

As the clinical community and the public at large become more educated about the prevalence of adult attention-deficit/hyperactivity disorder (ADHD), the pharmacotherapeutic options for the treatment of ADHD in adults continue to expand. As the symptoms of ADHD are recognized more often as continuing into adulthood, the amount of data available for both approved and novel treatment options continues to grow. In order for clinicians to make informed choices regarding treatment, it is necessary that they be educated with the latest information on the pharmacotherapeutic options available for adult ADHD patients, and the impact of treatment on patient quality of life.

LEARNING OBJECTIVES

After completing this activity, participants should be able to:

- Define the burden of ADHD in adults
- Outline the latest data on the efficacy and safety of stimulant and nonstimulant pharmacologic options for adult ADHD
- Describe the impact of pharmacologic treatment on the quality of life of adults with ADHD

Release Date: October 5, 2006

Expiration Date: October 5, 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. Murphy: Speakers bureau—Ortho-McNeil Inc

Planning Committee Kay Weigand, University of Cincinnati College of Medicine, Office of Continuing Education, and Kristin Dickie, Rosemary Hodgson, 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 uses of drugs or devices are discussed: the use of modafinil in the treatment of adult ADHD.

GRANT SUPPORT

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Pharmacologic Management of Adult ADHD: Exploring the Balance of Treatment Efficacy and Adverse Events

Approximately 4.4% of the adult population in the United States has attention-deficit/hyperactivity disorder (ADHD).¹ However, these rates may be underestimated due to a lack of age-appropriate diagnostic criteria. Some estimates suggest that up to 70% of children with ADHD will continue to be symptomatic as adults.² Even though it is a common condition, ADHD is often undiagnosed in adults.³

ADHD can cause a pattern of chronic and pervasive impairment in multiple life domains and significantly impact the quality of life of patients. Adults with ADHD often demonstrate impulsiveness, inattention, easy distractibility, difficulty following tasks through to completion, and deficits in executive functioning, planning, forethought, and working memory. They also have higher rates of criminality and car accidents than those without ADHD, and their symptoms often lead to poor job performance, lower occupational status, and problems with social skills.^{2,4} Research has also shown that they change jobs more frequently, have higher divorce and separation rates, and lower global marital satisfaction rates than their non-ADHD peers.^{4,5}

ADHD is also associated with a high prevalence of comorbidities. In a study of ADHD in adults based on data derived from the National Comorbidity Survey Replication, ADHD was frequently found in combination with other comorbid conditions.¹ Among respondents with ADHD, 18.6% reported a diagnosis of major depressive disorder in the 12 months prior to the survey, and 38.3% reported any mood disorder during that time. Respondents also reported a 47.1% prevalence of any anxiety disorder and a 15.2% prevalence of any substance use disorder during the 12 months prior to the survey. Only 10.9% of the respondents with ADHD had been treated for their ADHD symptoms in the 12 months prior to the interview.¹

Lastly, ADHD has an economic impact as well. Data reviewed by Biederman et al showed that when medical costs—inpatient, outpatient, and prescription drug costs—were compared for ADHD adults (n = 2292) and a matched non-ADHD cohort, the ADHD cohort incurred greater expense. The medical costs of the ADHD cohort were approximately twice those of the non-ADHD group over a 3-year period ($P < .01$), after controlling for the cost of medical and psychiatric comorbidities.⁶

Despite the negative and costly consequences of ADHD symptoms in adults, the majority of adults with ADHD remain untreated.¹ Many physicians have little formal training in the assessment of ADHD, and one study showed that only approximately 35% of primary care physicians surveyed diagnose adults with ADHD without consulting a specialist, with only 5% indicating a willingness to diagnose and treat adults with ADHD.⁷ However, this study indicated that 85% of physicians said that they would be willing to diagnose and treat ADHD in adults if there were an easy-to-use, validated screening tool available

for use.⁷ In a survey on treatment patterns, most patients had self-referred for treatment, and 56% of those found to have ADHD indicated that they had previously sought help for the symptoms without being diagnosed.⁸

Another complication to successfully managing ADHD in adults is that many adult patients with ADHD do not adhere to prescribed treatment regimens. In a comparison study designed to assess treatment compliance, rates of compliance for treatment of diabetes (thiazolidinedione, rosiglitazone, and insulin glargine), hypercholesterolemia (statin drugs), and ADHD (the stimulants mixed amphetamine salts, extended release [MAS-XR], and methylphenidate [MPH] modified release) were measured.⁹ Most patients were compliant for approximately 3 months after the initial prescription for these medications, but by the 7th month, compliance rates with all medications were low (rosiglitazone 33.4%, insulin glargine 17.6%, statin drugs 26.0%-30.1%, MAS-XR 22.9%, and MPH modified release 23.5%).⁹ Data indicate that ADHD patients tend to be more compliant with extended-release formulations because of convenience, but that these formulations are more likely to be reserved for patients with more severe symptoms.¹⁰

This *First Report*[®] will review results from studies in adults with ADHD, highlighting the studies individually as they each examine medication efficacy, safety, and tolerability, and the impact of pharmacotherapy on quality-of-life measures. The studies discuss data on both stimulants and nonstimulants for the treatment of adult ADHD.

Treatment has been found to minimize the negative impact of the symptoms of ADHD, leading to improved daily functioning and quality of life for these patients. While most research on ADHD has been conducted in children, more data on the symptoms of ADHD in adults and the response to therapy have become available in the past 2 years.

PHARMACOLOGIC TREATMENT OPTIONS

In a survey of current treatment of ADHD, 91% of psychiatrist-treated ADHD patients and 78% of primary care physician-treated ADHD patients were prescribed ADHD medication; stimulant medication was the treatment of choice in 84% of the 854 cases reviewed.⁸

In a study to assess community practice patterns, a study of pharmacy claims compared demographic and clinical characteristics of adults who were treated with extended-delivery preparations compared to those who were treated with immediate-release (IR) formulations.¹⁰ Extended-delivery preparations were used in 41.4% of the patients. These patients were slightly younger (mean = 31.1 versus 32.6 years) and were significantly more likely to have hyperactivity symptoms than patients started on IR formulations (44.1% on extended-delivery preparations versus 39.5% on IR, $P < .0001$).¹⁰ In addition, patients treated with extended-delivery preparations were

more likely to have used inpatient and emergency department services, mental health services, and to have had treatment for substance abuse in the 6 months prior to the initiation of therapy than patients treated with IR formulations.¹⁰

The available Food and Drug Administration (FDA)-approved stimulants include MAS, MPH, dextroamphetamine, and dexamethylphenidate in various formulations. Typical side effects include nervousness, sleep disturbance, appetite suppression, nausea, weight loss, headache, tachycardia, and abdominal pain.¹¹⁻¹⁵ Methylphenidate and dexamethylphenidate should be used with caution in patients with hypertension¹¹⁻¹³ and MAS and dextroamphetamine should not be used in patients with structural cardiac abnormalities, according to package inserts.^{14,15} Labeling for stimulants also note they should not be used in patients with marked anxiety, tension, and agitation.¹¹⁻¹⁵ Recently, the labeling for dextroamphetamine was updated to include a warning that use of the agent may exacerbate symptoms of behavior disturbance and thought disorder in patients with preexisting psychotic disorders, and that treatment-emergent psychotic or manic symptoms may result from use at usual doses of the agent in children and adolescents without a prior history of psychotic illness or mania.¹⁵

Atomoxetine is a selective norepinephrine reuptake inhibitor that is the only nonstimulant agent with FDA approval for the treatment of ADHD. Side effects associated with atomoxetine use include headache, dry mouth, insomnia, nausea, and appetite suppression.¹⁶ Atomoxetine use is cautioned in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease, according to the package insert.¹⁶ Atomoxetine has also been linked to increased suicidal ideation and rare cases of severe liver injury; patients should be monitored closely for such symptoms.¹⁶

Modafinil is approved for the treatment of narcolepsy, and it has recently been studied in clinical trials as off-label use for the treatment of ADHD. Modafinil selectively improves neuropsychological task performance, possibly through improved inhibitory control.¹⁷ A randomized, double-blind, placebo-controlled, crossover study of 20 adults with ADHD demonstrated improved cognitive function in short-term memory, visual memory, spatial planning, and stop-signal motor inhibition with modafinil treatment.¹⁸ However, due to safety concerns based on a suspected case of Stevens Johnson syndrome, 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 further development of the agent for the treatment of ADHD.¹⁹

EFFICACY OF TREATMENT OPTIONS

Recent research supports the efficacy of stimulant medication for use in adult patients with ADHD. In a 24-month, open-label extension of a 4-week, multicenter, double-blind, placebo-controlled, parallel-group, forced-dose escalation study to assess the safety and effectiveness of MAS-XR, 223 adult patients were treated on doses that were titrated to 60 mg/day. ADHD symptoms improved significantly based on ADHD Rating Scale IV (ADHD-RS-IV) scores ($P<.001$), and the improvement was sustained for up to 24 months.⁶ Of the total treated patients, 3.1% discontinued therapy due to lack of efficacy. An analysis of data from the 30-week, open-label, multicenter, Quality of Life, Effectiveness, Safety, and Tolerability (QuEST) trial evaluated the efficacy of MAS-XR.²⁰ At 10 weeks, all 725 adults enrolled in the study demonstrated sustained improvement in ADHD symptoms measured on the ADHD-RS-IV, hyperactivity/impulsivity subscale, and inattentive subscale.²⁰

The efficacy of the osmotic release oral system (OROS)-MPH in doses up to 1.3 mg/kg/day was studied in a randomized, 6-week, placebo-controlled, parallel-design study of 141 adults with ADHD.²¹ At the end point, 66% of the patients on OROS-MPH and 39% of patients on placebo attained a response; response was defined as much improved or very much improved on the Clinical Global Impression-Improvement scale and a greater than 30% reduction in scores on the Adult ADHD Investigator System Report Scale.²¹

The efficacy of psychotherapy, dextroamphetamine, and/or paroxetine (selective serotonin reuptake inhibitor) has also been studied in adults with ADHD. In a randomized, placebo-controlled, prospective trial, 98 adult patients with ADHD received psychotherapy combined with dextroamphetamine, paroxetine, both, or placebo for 20 weeks.²² ADHD symptoms were significantly lower in patients treated with dextroamphetamine ($P=.012$). Paroxetine demonstrated no effect on ADHD symptoms. ADHD symptoms responded to dextroamphetamine or combined treatment, and mood-related symptoms responded to paroxetine or combined treatment. However, patients treated with both paroxetine and dextroamphetamine did not show greater overall improvement over single-agent treatment.²²

A small, double-blind, placebo-controlled, multiple-crossover pilot study of adult patients with substance abuse disorders and ADHD was designed to determine the benefits of treatment with MPH.²³ Twenty-five adults receiving in-patient treatment for substance abuse were randomized to either low-dose MPH (up to 0.6 mg/kg/day) or placebo in 2-week phases that alternated over 8 weeks.²³ ADHD symptoms on the ADHD-RS-IV were improved in 36% of those treated with MPH; 20% with placebo. The study investigators concluded that MPH was no more effective than placebo when used at these very low doses.²³

The impact of a lifetime history of any mood or anxiety diagnosis upon response to dextroamphetamine or paroxetine was examined in a post-hoc moderator analysis of data from a double-blind, randomized, placebo-controlled prospective trial of 62 patients. A lifetime history of internalizing disorder (diagnosed through a structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) was associated with a significantly attenuated response of symptoms of ADHD ($P<.05$) and diminished clinician ratings of improvement ($P<.05$) with dextroamphetamine.²⁴ The data suggest that some patients who have a history of a mood or anxiety disorder may respond less robustly to stimulant treatment, in this case dextroamphetamine, than those with no history of these disorders.

A randomized, double-blind, multisite, placebo-controlled, prospective trial randomized 48 adult patients with ADHD to problem-focused therapy (PFT); ie, education about ADHD and effective coping strategies) plus placebo or PFT plus dextroamphetamine in an analysis of the efficacy of psychotherapy.²⁵ Both groups showed improved ADHD symptoms over the first 20 weeks of the study ($P<.001$ for both); however, the onset of improvement was earlier in the PFT-dextroamphetamine group. In addition, the PFT-dextroamphetamine group demonstrated persistent benefit, while the PFT-placebo group had deterioration of symptom control after week 10.²⁵

The effects of MAS-XR on the speed and accuracy of neurocognitive function in young adults were studied in 14 adults (19-25 years) who were enrolled in a 6-week, randomized, single-center, double-blind, placebo-controlled, 2-way crossover study.^{26,27} Patients received either placebo for 3 weeks and then treatment for 3 weeks or vice versa. Performance on all tested variables, including 5 speed measures and

4 accuracy measures, improved with treatment with MAS-XR compared to placebo. The order of treatment influenced the outcome: those initially treated with MAS-XR had persistent improvement in scores after being changed to placebo (practice effect), whereas the group who started on placebo showed improved accuracy after being switched to treatment.^{26,27}

To determine the effect of atomoxetine on symptoms of emotional dysregulation (ie, responding in a manner that is considered outside the normal range of emotions for a given situation) in adults with ADHD, data on 529 patients from 2 placebo-controlled outpatient studies were analyzed.²⁸ The authors found that 32% of adults studied had emotional dysregulation. Using the rating scale devised by the authors, patients with emotional dysregulation treated with atomoxetine improved by 42% compared to 19% of patients who were treated with placebo ($P=.001$).²⁸ Clinical Global Impression-Severity (CGI-S) scores in patients on atomoxetine improved by 20% compared to 10% in those on placebo ($P=.001$).²⁸

Data from 2 identically designed studies comparing atomoxetine to placebo were evaluated in a post-hoc analysis to evaluate efficacy in younger adults, ages 18 to 24 ($n = 55$), and older adults, ages 26 to 77 ($n = 481$).²⁹ Atomoxetine resulted in significantly greater benefits in younger and older adults compared to placebo, as measured by changes in the Conners' Adult ADHD Rating Scale Total ADHD Symptom score ($P=.041$, $P<.001$, respectively) and the CGI-S ($P=.006$, $P<.001$).

SAFETY AND TOLERABILITY OF PHARMACOLOGIC TREATMENT

Reports continue to explore the tolerability and safety of treatments for ADHD and provide important information for appropriately prescribing and managing ADHD treatment regimens. In the 24-month study of MAS-XR by Biederman et al, safety was assessed in addition to the efficacy analysis already discussed.⁶ Doses were titrated to 60 mg/day on the basis of therapeutic efficacy. Of the 147 patients (66%) who discontinued the study before study end (prior to receiving 24 months of therapy), 48 patients (21.5%) withdrew because of adverse events, occurrences that patients spontaneously reported over the course of therapy. Adverse events that occurred during treatment—not treatment related or possibly treatment related based on investigator judgment—declined over the course of treatment from 84.3% of patients reporting 700 side effects in month 1, to 10 patients (12.7% of 79 patients still in the study) reporting 16 side effects at month 24.⁶ The most common adverse events related to treatment were agitation, anorexia, dry mouth, headache, insomnia, nervousness, and weight loss.⁶ A total of 11 serious adverse events were reported, with only 1 serious adverse event (depression/suicidal ideation secondary to bipolar disorder) being considered treatment related. One subject withdrew from the study due to tachycardia, and another due to hypertension.⁶

In the randomized trial of OROS-MPH detailed in the efficacy section, the safety analysis found a small increase in systolic blood pressure (SBP), diastolic blood pressure (DBP) (3.5 ± 11.8 mm Hg and 4.0 ± 8.5 mm Hg, respectively), and heart rate (4.5 ± 10.5 beats per minute) in patients treated with OROS-MPH compared to those treated with placebo.²¹ The authors noted that because of the potential for increases in blood pressure and heart rate, patients should have their blood pressure monitored for changes over the course of their stimulant treatment.

In a study of cardiovascular effects in patients treated with MAS-XR,

223 adult patients treated with MAS-XR were evaluated at baseline, weekly, and then monthly for DBP, SBP, and pulse rate for ≤ 24 months.³⁰ Electrocardiograms were done at baseline, weekly, and then every 3 to 6 months. Mean changes from baseline were DBP 1.3 ± 9.2 mm Hg, SBP 2.3 ± 12.5 mm Hg, and pulse rate 2.1 ± 13.4 beats per minute, none of which reached statistical significance. There were no serious adverse events. The authors noted that although the cardiovascular events were minimal, patients should be periodically monitored.³⁰

In the randomized study of the effect of MAS-XR on neurocognitive accuracy and speed, tolerability measures were reported in terms of adverse events versus placebo.^{26,27} The most commonly observed adverse events with treatment compared to placebo were appetite suppression (50% versus 0%), decreased weight (25% versus 6%), and dry mouth (19% versus 0%). Less common adverse events included headache, anger, bruxism (grinding of teeth), insomnia, and irritability.^{26,27}

In a recently published Institutional Review Board-approved chart review, the combination of atomoxetine and stimulant therapy was well tolerated in most patients (75.9%).³¹ The most commonly reported side effects included insomnia, irritability, dysphoria, agitation, and decreased libido. Comorbidities as well as the dose of stimulant used did not significantly affect tolerability.³¹

A randomized, double-blind, multicenter study of 218 adults was designed to compare the safety and tolerability of atomoxetine 80 mg once daily with 40 mg twice daily.³² The study reported the overall incidence for any 1 type of adverse event was low, and there was no significant difference between the groups for dry mouth, insomnia, and erectile dysfunction. Nausea was significantly lower in the once-daily group (16.4% versus 32.4%, $P=.007$).³²

The post-hoc analysis by Durell et al mentioned previously also revealed adverse events data for atomoxetine in adults ages 18 to 24 and ages 26 to 77 versus placebo.²⁹ No significant difference between the smaller-size younger group and placebo was evident in any of the evaluated treatment-emergent adverse events. In the older group, significant differences were found between atomoxetine and placebo for the following: dry mouth (15 in the placebo group and 53 in the treatment group, $P<.001$), nausea (10 versus 29, $P=.002$), decreased appetite (8 versus 25, $P=.003$), erectile dysfunction (2 versus 17, $P<.001$), constipation (10 versus 23, $P=.30$), dizziness (4 versus 15, $P=.017$), hyperhidrosis (1 versus 10, $P=.011$), and decreased libido (4 versus 16, $P=.010$). The study also collected changes in blood pressure measurement from baseline. Data from the older group showed a significant change from baseline with atomoxetine compared to placebo, $P=.024$, but not with the younger patients. The authors did

Initial data

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of ADHD

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note, however, that the post-hoc analysis was limited by the relatively small young adult sample size.²⁹

QUALITY OF LIFE CHANGES WITH TREATMENT

In the 10-week interim analysis of the intent-to-treat patients in the QuEST trial by Goodman et al (N = 702), with MAS-XR treatment, quality-of-life measures were found to be improved in areas of general health, physical and mental health, vitality, and social, emotional, and physical role functioning based on data from the 36-Item Short Form Health Survey version 2 ($P < .0001$).²⁰

Another analysis reviewed data on satisfaction with treatment using the Medication Satisfaction Survey during the first 10 weeks of the QuEST trial for the 77 patients of the intent-to-treat group who were previously treated with a short-acting stimulant.³³ At baseline, the response to the survey statement of, "Overall, I am satisfied with taking this medication," was 48.1% of subjects strongly agreed/agreed. Other survey answers included 41.6% of patients who strongly agreed/agreed that they were satisfied with their dosing schedule, and 39% strongly agreed/agreed that they rarely missed doses.³³ After 10 weeks of treatment with MAS-XR, 72.8% strongly agreed/agreed that overall they were satisfied with taking the medication, and 87% chose the response strongly agreed/agreed to being satisfied with the once-daily dosing, and 87.8% reported that they rarely missed doses. Patients also reported improved satisfaction in the control of symptoms, including the duration of effect (63.7%), behavior (72.8%), attention (68.9%), and social interactions (52%).³³

Patients from the QuEST trial were also tested for quality-of-life improvement with treatment using the ADHD Impact Module-Adult, a 66-question, patient-completed survey developed from cli-

nician interviews, patient interviews, and literature review.³⁴ The overall quality-of-life ratings improved significantly in all 4 treatment groups (treatment naïve, previous stimulant treatment, previous nonstimulant treatment, all subjects; $P < .0001$). The scores improved in all six subscales: living with ADHD; general well-being; performance and daily functioning; relationships and communication; bothersomeness and concern; and daily interference ($P < .0001$). The improvements became apparent by week 2 and were sustained through week 10, regardless of previous treatment.³⁴

To make available a validated adult ADHD-specific quality-of-life measure, the 29-item Adult ADHD Quality-of-Life Scale recently was developed, based on established methods for developing patient-reported outcome scales.³⁵ The scale consists of 4 sections: life productivity, psychological health, relationships, and life outlook. The Adult ADHD Quality-of-Life Scale was evaluated for validity through administration of the scale to 989 adults in a retrospective cohort study, followed by psychometric validation, which included the evaluation of reliability, validity, and responsiveness using an *a priori* statistical analysis plan. Internal consistency was 0.93 for the overall scale, supporting its validity. Developers suggest that the scale may facilitate future research in quality-of-life issues.³⁵

CONCLUSION

Current and emerging data support that available treatments for adults with ADHD (stimulant and nonstimulant) are safe and effective for most people. Initial data suggest that the improvement of direct symptoms of ADHD positively impact quality-of-life measures. Progress is being made in understanding the prevalence, characteristics, and consequences of ADHD in adults; and future studies will continue to look at areas of cost and impact of treatment on quality of life, comorbidities, and symptom control. ■

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2006-183-2