

Adult ADHD: Issues and Answers

CME Newsletter of the Adult ADHD Program,
Department of Psychiatry, NYU School of Medicine

Adult ADHD and Sleep Complaints— How the Diagnoses Can Overlap

Attention-deficit/hyperactivity disorder (ADHD) and sleep disorders can overlap and confuse the diagnosis of a patient who exhibits particular symptoms. Sleep disorders such as insomnia, sleep apnea, and narcolepsy can increase ADHD symptoms,¹ whereas ADHD can result in sleep disturbances whether they are part of the condition or a side effect of medication. Regardless, both sleep disorders and ADHD can cause cognitive impairment. Recent studies have focused on sleep disorders and ADHD with an emphasis on sleep-disordered breathing (SDB), restless legs syndrome (RLS), sleep quality in patients with ADHD, and primary hypersomnia.

Sleep-Disordered Breathing in ADHD

New evidence shows that sleep disorders can be found in adults with ADHD who report poor sleep quality, daytime fatigue, or both traits, and that these traits should not be simply attributed to ADHD status or medication effects alone. A Harvard University-based pilot study by Surman and colleagues identified SDB using polysomnography and sleep quality assessments in 6 adults with carefully diagnosed ADHD (2 with inattentive; 4 with combined) with comorbid sleep fragmentation problems (early/middle insomnia, snoring, apnea, daytime drowsiness).² The premise for the study was that the prevalence of ADHD and SDB requires clarification of the contribution of SDB in individuals diagnosed with ADHD (see Sidebar - What is SDB?). The polysomnography analysis found clear evidence of SDB in all patients. Although it is possible that SDB was the primary cause of the symptoms diagnosed as ADHD in some of the individuals in this relatively small study, these conditions are not mutually exclusive. In fact,

they may be comorbid in some adults and should be treated separately because sleep fragmentation itself can impair attention, mood, and memory. Clarification of whether comorbidity between ADHD and SDB occurs due to chance alone would require a larger study in both SDB and ADHD populations. This study does provide evidence that SDB can be present in adults with rigorously diagnosed ADHD who also express sleep complaints and highlights the potential importance of identifying comorbid sleep disorders, and particularly SDB in ADHD participants.

ADHD and Restless Legs Syndrome

Restless legs syndrome occurs in approximately 2.5% to 10% of the population.³ Patients with RLS often have severe insomnia because of leg discomfort and periodic limb movements that interfere with sleep onset. Attention deficit/hyperactivity disorder and RLS are linked by 2 characteristics: sleep disruption and hyperactivity. The latter has been seen in schoolchildren with RLS who are unable to remain seated because of the need to walk around to get rid of their leg discomfort.⁴ Thus, it would appear that hyperactivity can lead to inattention through the mechanism of leg discomfort. Wagner and colleagues from Rutgers School of Pharmacy did a study to determine the occurrence of symptoms of ADHD in adults with RLS as compared with ADHD controls with insomnia and non-ADHD controls.¹ Patients with RLS had significantly more ADHD symptoms than insomnia patients or controls using age-adjusted total DSM-IV ADHD scores [See Table 1]. The RLS symptom severity was greater in RLS and ADHD symptoms than in those without ADHD ($P < .04$). Thus, while ADHD symptoms are more common in patients with RLS than in patients with insomnia or controls, RLS leg discomfort or poor sleep quality may lead to hyperactivity and lack of concentration. Alternatively, RLS and ADHD may be part of a single-symptom complex, and

Table 1—Percentage of Subjects Meeting Criteria for ADHD Based on Total Age-Adjusted DSM-IV Symptom Scale Scores¹

Variable	RLS	Insomnia	Controls
Inattention and hyperactivity	26%*	6%	5%
Inattention	24%*	9%	5%
Hyperactivity/impulsivity	32%*	6%	4%

* $P < .01$ for patients with RLS compared with patients with insomnia and controls.

Sponsored by:



Supported by an
unrestricted educational grant from:



Statement of Need

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood; incidence ranges from 5% to 10% among school-aged children. Up to 50% of children with ADHD continue to have ADHD-related problems during their adult years. In addition, many ADHD cases are first diagnosed only after patients have reached adulthood. Adults with ADHD may experience significant functional problems, such as job difficulties, academic underachievement, troublesome relationships with family and peers, and low self-esteem. Diagnosing ADHD in adults can be difficult, and even when the diagnosis is made—available medications are often not used to treat the disorder, or medication management varies widely across communities and among physicians. Recent findings and research into the use of new chemical entities such as amphetamine CX717 and NS2359 continue to expand the understanding of ADHD in these patients and its associated comorbidities. Brain research into binding sites and transporters also is enhancing the clinician's understanding of how medications work to effect change in patients with ADHD.

Evidence has revealed that sleep disorders such as insomnia, sleep apnea, and narcolepsy can also confuse the diagnosis of ADHD. Each has been associated with daytime cognitive impairment, which could be interpreted as inattention. In addition to sleep disorders, conditions such as restless legs syndrome (RLS) have been shown to lead to insomnia and a decrease in sleep quality as well as discomfort that is only remedied by constant movement such as that seen in hyperactivity.

Often, the use of a single agent for the management of ADHD is not an option due to partial responsiveness, dose-limiting side effects, preexisting medical conditions, and/or comorbid diagnoses. Combination therapy with agents both approved and some not approved for the treatment of ADHD are being investigated, leading to new recommendations for the appropriate management of the core impairments: inattention, hyperactivity, and impulsivity.

Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163:716-723.

Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:629-640.

Richards TL, Dreffbacher JL, Rosen LA, Barkley RA, Rodricks T. Driving anger and driving behavior in adults with ADHD. *J Atten Disord*. 2006;10:54-64.

Barkley RA, Guevremont DC, Anastopoulos AD, DuPaul T, Shelton TL. Driving-related risks and outcomes of attention deficit hyperactivity disorder in adolescents and young adults: a 3- to 5-year follow-up survey. *Pediatrics*. 1993;92:232-238.

Fischer M, Barkley RA, Smallish L, Fletcher K. Hyperactive children as young adults: driving abilities, safe driving behavior, and adverse driving outcomes. *Accid Anal Prev*. 2006 Aug 16; [Epub ahead of print].

Safren SA, Otto MW, Sprich S, Wineret CL, Wilens TE, Biederman J. Cognitive-behavioral therapy for ADHD in medication-treated adults with continued symptoms. *Behav Res Ther*. 2005;43:831-842.

Wagner ML, Walters AS, Fisher BC. Symptoms of attention-deficit/hyperactivity disorder in adults with restless legs syndrome. *Sleep*. 2004;27:1499-1504.

Surman CB, Thomas RJ, Alvard M, Pagano C, Biederman J. Adults with ADHD and sleep complaints: a pilot study identifying sleep-disordered breathing using polysomnography and sleep quality assessment. *J Atten Disord*. 2006;10:550-555.

Garcia-Borreguero D, Egatz R, Winkelmann J, Berger K. Epidemiology of restless legs syndrome: the current status. *Sleep Med Rev*. 2006;10:153-167.

Walters AS, Mandelbaum DE, Lewin DS, et al. A long-term open-label study of dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. Dopaminergic Therapy Study Group. *Pediatr Neurol*. 2000;22:182-186.

Oosterloo M, Lammers GJ, Overeem S, de Noord I, Kooij JJ. Possible confusion between primary hypersomnia and adult attention-deficit/hyperactivity disorder. *Psychiatry Res*. 2006;143:293-297.

Moore CM, Biederman J, Wozniak J, et al. Differences in brain chemistry in children and adolescents with attention deficit hyperactivity disorder with and without comorbid bipolar disorder: a proton magnetic resonance spectroscopy study. *Am J Psychiatry*. 2006;163:316-318.

Adler LA, Stein M, Mansbach H. Treatment of adult ADHD with the novel AMPAMINE CX717 [poster]. Presented at the 53rd Annual Meeting of the American Academy of Adolescent and Child Psychiatry, October 25-29, 2006, San Diego, California.

Wilens TE, Biederman J, Adler LA, et al. A controlled trial of the efficacy and safety of NS2359 in adults with ADHD [poster]. Presented at the 53rd Annual Meeting of the American Academy of Adolescent and Child Psychiatry, October 25-29, 2006, San Diego, California.

Learning Objectives

After completing this activity, you should be better able to:

- Identify common associated sleep disturbances that may affect the diagnosis of ADHD
- Summarize several treatment strategies that may be necessary to optimize the management of a patient with ADHD
- Evaluate recent research on the treatment of adult ADHD to advance the treatment and management strategies for adult ADHD

Method of Participation

Read this newsletter, complete the CME Posttest Answer Form and Activity Evaluation Form, and fax or mail the forms to Medical Education Resources, Inc. at the address listed. You will receive a certificate by fax or mail. There is no certificate processing fee.

Intended Audience

This activity was developed for psychiatrists, primary care physicians/internists, neurologists, and psychologists.

Effective Dates

Released: December 2006
Expires: November 30, 2007

Accreditation/Designation Statements

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 Medical Education Resources, Inc. and MedLearning Inc. Medical Education Resources, Inc. is accredited by the ACCME to provide continuing medical education for physicians.

Medical Education Resources, Inc. designates this educational activity for a maximum of .75 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Sponsorship and Support

This activity is jointly sponsored by Medical Education Resources, Inc. and MedLearning Inc. The activity is supported by an unrestricted educational grant from Shire.

Faculty Author

Lenard A. Adler, MD
Director, Adult ADHD Program
Associate Professor
Departments of Psychiatry and Neurology
New York University School of Medicine
New York, New York

Financial Disclosure Statements

In accordance with the ACCME's Standards for Commercial Support, all CME providers are required to disclose to the activity audience the relevant financial relationships of the planners, teachers, and authors involved in the development of CME content. An individual has a relevant financial relationship if he or she has a financial relationship in any amount occurring in the last 12 months with a commercial interest whose products or services are discussed in the CME activity content over which the individual has control. Disclosures are as follows:

Dr Adler has received honoraria from Medical Education Resources, Inc. for his assistance as editor. In addition, he has disclosed the following relevant financial relationships:

Dr Adler receives grant/research support from Abbott Laboratories, Bristol-Myers Squibb Company, Cortex Pharmaceuticals, Inc., Eli Lilly and Company, Johnson & Johnson, McNeil Consumer and Specialty Pharmaceuticals, Merck & Co., Inc., Novartis Pharmaceuticals, Pfizer Inc. and Shire US Inc. He is a consultant for Abbott Laboratories, Bristol-Myers Squibb Company, Cephalon Inc., Cortex Pharmaceuticals, Inc., Eli Lilly and Company, Johnson & Johnson, McNeil Consumer and Specialty Pharmaceuticals, Merck & Co., Inc., Novartis Pharmaceuticals, Pfizer Inc. and Shire US Inc. Dr Adler has participated in speakers' bureaus for Eli Lilly and Company, Johnson & Johnson, McNeil Consumer and Specialty Pharmaceuticals, Novartis Pharmaceuticals, Pfizer Inc. and Shire US Inc.

The staff of Medical Education Resources, Inc. has nothing to disclose.

The staff of MedLearning Inc. has nothing to disclose.

Use of Brand and Generic Names

Brand names of products for treating attention-deficit/hyperactivity disorder (ADHD) are used throughout this continuing medical education (CME) activity so that participants can distinguish among the many different formulations (duration of action, delivery system) of products with the same generic name.

Unlabeled Use Disclosure Statement

Participants are advised that this CME activity will contain references to unlabeled/unapproved/investigational uses of drugs to treat ADHD.

Disclaimer

The opinions expressed in this activity are those of the author and do not necessarily reflect those of Medical Education Resources, Inc., MedLearning Inc., or Shire. Please consult the appropriate package insert for full prescribing information on all drug therapies discussed.

Copyright © 2006 Medical Education Resources, Inc. All rights reserved.

dopaminergic deficiency may play a role in both disorders. The bottom line: Patients with RLS should be screened for ADHD symptoms and patients with ADHD should be screened for RLS symptoms.

Is it Adult ADHD or Primary Hypersomnia?

While adults referred to sleep clinics may be diagnosed with ADHD and treated accordingly, sometimes the opposite situation occurs. A Dutch study by Oosterloo et al illustrated the possibility of diagnostic confusion between hypersomnias of central origin (eg, narcolepsy and idiopathic hypersomnia [IH]) and adult ADHD.⁵ This study, which included 67 patients with narcolepsy, 7 with IH, and 61 with ADHD, revealed that 19% of the IH patients fulfilled the self-reported criteria for ADHD in adulthood, compared with 77% of the patients with ADHD. Excessive daytime sleepiness, as measured by the Epworth Sleepiness Scale, was found in 38% of the patients with ADHD compared with 96% of the patients with IH. In patients with ADHD, inattention scores correlated with the excessive daytime sleepiness score. Thus, awareness of possible diagnostic confusion between narcolepsy or IH and adult ADHD is essential. The high percentage of symptom overlap found in the study raises questions about possible misdiagnoses of both conditions, comorbidity with sleep problems in adult ADHD, and the validation of the scales used. Whether the findings indicate pathophysiological overlap is not clear.

What is SDB?

Sleep-disordered breathing describes a group of disorders characterized by abnormalities of respiratory pattern (pauses in breathing) or the quantity of ventilation during sleep. Obstructive sleep apnea, the most common such disorder, is characterized by the repetitive collapse or partial collapse of the pharyngeal airway during sleep and the need to arouse to resume ventilation. Sleep is thus disrupted, yielding waking somnolence and diminished neurocognitive performance. Recently, epidemiological and pre-post treatment analyses have identified substantial morbidities that primarily affect the neurobehavioral systems. These morbidities include learning and cognitive deficits, and behavioral problems that resemble ADHD.

References

1. Wagner ML, Walters AS, Fisher BC. Symptoms of attention-deficit/hyperactivity disorder in adults with restless legs syndrome. *Sleep*. 2004;27:1499-1504.
2. Surman CB, Thomas RJ, Alvard M, Pagano C, Biederman J. Adults with ADHD and sleep complaints: a pilot study identifying sleep-disordered breathing using polysomnography and sleep quality assessment. *J Atten Disord*. 2006;9:550-555.
3. Garcia-Borreguero D, Egatz R, Winkelmann J, Berger K. Epidemiology of restless legs syndrome: the current status. *Sleep Med Rev*. 2006;10:153-167.
4. Walters AS, Mandelbaum DE, Lewin DS, et al. A long-term open-label study of dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. Dopaminergic Therapy Study Group. *Pediatr Neurol*. 2000;22:182-186.
5. Oosterloo M, Lammers GJ, Overeem S, de Noord I, Kooij JJ. Possible confusion between primary hypersomnia and adult attention-deficit/hyperactivity disorder. *Psychiatry Res*. 2006;143:293-297.

Case Study

Helen, aged 34, is a librarian with a history of ADHD inattentive subtype and generalized anxiety disorder (GAD), originally evaluated several years previously. Complaints at original presentation included inattention, easy distraction, misplacing items, losing track in conversations, forgetfulness, trouble with task completion, and procrastination. These symptoms impaired her both at work and at home (eg, task completion, procrastination) as well as socially (eg, trouble planning, missing parts of conversations). Generalized anxiety disorder symptoms at the time of original presentation included increased general worry with ruminative thoughts over perceived and real problems, especially at night, creating early and middle insomnia. No panic attacks or compulsions were noted. Mental status exam at time of original presentation was notable for affect constricted to anxious mood. No thought disorders, no psychotic symptoms, or suicidal or homicidal ideation were observed; patient was alert and fully oriented.

Helen was originally in supportive psychotherapy, which she continued. Trials of selective serotonin-reuptake inhibitors (SSRIs) and psychostimulants were ineffective in treating GAD and ADHD, either because of ineffectiveness (SSRI) or GAD exacerbation (stimulants). Both conditions were successfully treated with imipramine 250 mg/day.

However, long-standing issues with early and middle insomnia continued despite the soporific effects of the tricyclic. Successive trials of bedtime clonazepam 0.5 mg, ramelteon 8 mg, and eszopiclone 2 mg proved ineffective. Treatment was successful on an every-other-night basis with controlled-release zolpidem 12.5 mg. Helen reports that she knows that she will sleep well the following night even when she is not taking the hypnotic, which undercuts the anticipatory anxiety about sleep. She also reports improved attention now that sleep problems have been effectively treated.

Take-home points:

- Sleep problems can be antecedent to ADHD therapy
- Comorbid anxiety can complicate the clinical picture
- Successful therapy may take several attempts
- Anticipatory anxiety plays a role in insomnia
- Insomnia can impact attention problems

Guide to Using Combination Therapy in Adult ADHD

While clinical guidelines recommend monotherapy with stimulants or atomoxetine to treat ADHD, combination therapy with other types of medications is common practice according to recent information presented by Pohle and colleagues at the 2006 American Psychiatric Association.¹ While not outlined in any FDA-approved product information, the use of 2 or more medications for the management of ADHD symptoms may be necessary for some patients including those who have partial response, dose-limiting side effects, preexisting or treatment-induced disorders, and comorbid diagnoses.² In addition, much of what is known about the use of combination therapy comes from

the management of children with ADHD and the transferability of this experience to adult patients is the focus of attention for many clinicians.

Next issue: Risks of combination therapy

References

1. Pohle GM, Van Brunt DL, Ye W, et al. A retrospective claims analysis of polypharmacy in the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults. Poster presented at the 159th Annual Meeting of the American Psychiatric Association. Toronto, Ontario; May 23, 2006.
2. Adler LA, Reingold LS, Morrill MS, Wilens TE. Combination pharmacotherapy for adult ADHD. *Curr Psychiatry Reports*. 2006;8:409-415.
3. Allen AJ, Kurlan RM, Gilbert DL, et al. Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. *Neurology*. 2005;65:1941-1949.
4. Brown TE. Atomoxetine and stimulants in combination for treatment of attention deficit hyperactivity disorder: four case reports. *J Child Adolesc Psych*. 2004;14(1):129-136
5. Jaworowski S, Benarroch F, Gross-Tsur V. Concomitant use of atomoxetine and OROS-methylphenidate in a 10-year-old child suffering from attention-deficit/hyperactivity disorder with comorbid bipolar disorder and Tourette syndrome. *J Child Adolesc Psych*. 2006;16(3):365-370.

New Agents Show Promise in Adult ADHD

Novel agents are being evaluated in ADHD treatment. The efficacies of 2 such agents were presented at the 2006 American Academy of Adolescent and Child Psychiatry in San Diego.

Glutamate, the predominant neurotransmitter in the brain, is recognized by a number of receptor subtypes. The alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor mediates fast synaptic transmission in the central nervous system and is involved in a process known as long-term potentiation (LTP) which is believed to underlie the encoding of many types of memory. A reduced level of glutamate-mediated excitatory stimulation has been implicated in a number of disorders such as Alzheimer's disease and schizophrenia. Because glutamate is a measure of glutamatergic neurotransmission and, therefore, may also reflect changes in serotonin and dopamine pathways¹, its function in ADHD is also being investigated. AMPAKINE CX717 is a drug that can increase alpha-amino-3-hydroxy-5-methylisoxazolepropionic acid (AMPA) receptor activity. In a phase 2a study, the efficacy, tolerability, and safety of CX717 was evaluated in the treatment of 68 male adults with moderate-to-severe ADHD.² The randomized, double-blind, multicenter, 2-period crossover study compared 2 doses of CX717 (either 200 mg bid or 800 mg bid) with placebo. Each treatment period lasted 3 weeks separated by a 2-week washout period. CX717 800 mg bid was significantly more effective than placebo on the total ADHD-RS ($P=.002$) and on both the hyperactivity ($P=.017$) and inattentiveness ($P=.027$) subscales. The effects of the 200-mg bid dose were not different than that seen with placebo. No significant safety concerns or changes in cardiovascular parameters were observed with either dose. Sleep disturbances and headache were the most frequently reported adverse events.

Because adults with ADHD experience a wide range of dysfunctional behaviors including depression, researchers are

Issue: Partial ADHD Response

Often associated with trough drug serum levels of short-action medications

Short-acting stimulants:

- Work quickly (usually within 30 minutes)
- Limited duration of effect
- Requires multiple doses to cover the normal day

Long-acting stimulants:

- Mixed-amphetamine salts extended release (Adderall XR®) and d-methylphenidate (MPH) extended release (Focalin XR®) are both approved for the management of adult ADHD
- + May provide symptom relief for 8 to 14 hours

Atomoxetine (Strattera®)

- + Can ameliorate ADHD symptoms in once-daily dose, although the possibility exists of increased efficacy with twice-daily administration

Note: The use of a second agent (different class of medication) may substantially increase the duration and extent of therapeutic effect for partial responders.

Issue: Dose-Limiting Side Effects

Insomnia, restlessness, mood disturbances, decreased appetite, increased blood pressure

- Clonidine has been used in combination with stimulants to address symptoms of irritability and insomnia; however, both can affect appetite
- Atomoxetine has been shown to ameliorate common adverse effects of OROS-MPH (Concerta®) when it replaced afternoon therapy
- The effects of atomoxetine appear to be additive to stimulant therapy without increasing the incidence of adverse events⁴
- Clonidine has been found to be a useful agent for ADHD-associated sleep disturbances*

*Watch for potential cardiovascular side effects

Issue: Comorbidities

Motor Tics (can occur and/or emerge with stimulant use for ADHD)

- Clonidine or an atypical antipsychotic may minimize tics if they emerge
- Atomoxetine has not been shown to exacerbate tic disorder when used in combination or as monotherapy³ and preliminary case report data has shown positive effects when used in combination in patients partially responsive to MPH⁴

Mood disorders, anxiety disorders, substance use disorders (SUDs), impulse control disorders

- Drug dependence, dysthymia, and bipolar disorder (BPD) are the most prevalent comorbid diagnoses in adults
- In BPD, if justification for using 2 medications exists, first stabilize mania (eg, divalproex sodium) and then treat ADHD symptoms.

seeking molecules that can provide efficacy from several vantage points, that is, agents with predominately dopaminergic, noradrenergic, or mixed effects that can impact cognition or ADHD. NS2359, a dopamine/noradrenaline- and serotonin-reuptake inhibitor, was assessed in an 8-week randomized study in adults with ADHD.³ Overall, no significant difference between NS2359 and placebo was seen in the reduction of the investigator-rated ADHD-RS or in responders for the combined subtype. However, in a post hoc analysis, those with the inattentive subtype of ADHD, a significantly ($P < .01$) larger proportion of responders (>30% change in total ADHD-RS) were found in the NS2359 treatment (41.2%) compared with placebo (7.4%). The most commonly reported adverse events were insomnia and headaches. Given the response seen in patients with the inattentive subtype, larger, dose-ranging studies with NS2359 are warranted.

References

1. Moore CM, Biederman J, Wozniak J, et al. Differences in brain chemistry in children and adolescents with attention deficit hyperactivity disorder with and without comorbid bipolar disorder: a proton magnetic resonance spectroscopy study. *Am J Psychiatry*. 2006;163:316-318.
2. Adler LA, Stein M, Mansbach H. Treatment of adult ADHD with the novel AMPAKINE CX717 [poster]. Presented at the 53rd Annual Meeting of the American Academy of Adolescent and Child Psychiatry; October 25-29, 2006; San Diego, California.
3. Wilens TE, Klint T, Adler LA, et al. A controlled trial of the efficacy and safety of NS2359 in adults with ADHD [poster]. Presented at the 53rd Annual Meeting of the American Academy of Adolescent and Child Psychiatry; October 25-29, 2006; San Diego, California.

Journal Reviews

Atomoxetine Improves Quality of Life

As with any psychotropic medication, does efficacy come at the expense of quality of life (QOL)? Atomoxetine is a selective norepinephrine-reuptake inhibitor that was approved in the United States in 2002 as the only nonstimulant agent for the treatment of ADHD in children, adolescents, and adults. A new study by Adler and colleagues uses data from a clinical trial of atomoxetine in adults with ADHD¹ to incorporate a measure of health-related QOL (the Medical Outcomes Study 36-item short-form health survey [SF-36]) as part of the overall assessment of the success of this relatively new treatment.² The primary outcome measure for ADHD symptoms was the Conners Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS) ADHD total symptom score. In agreement with previous studies, adult patients with ADHD treated with atomoxetine at typical doses showed significant amelioration of their ADHD symptoms, as measured on the CAARS (improvement in ADHD total symptoms score, hyperactive/impulsive, and inattentive subscales; $P < .001$). At baseline, the measures of overall mental health (one aspect of QOL) of adult patients with ADHD were below the average level, as measured on the SF-36. Treatment with atomoxetine significantly improved the measures of the mental health component summary (vitality, social function, role emotional, mental health) and ameliorated ADHD symptoms. These data suggest that pharmacological intervention with atomoxetine not only ameliorates ADHD symptoms in adult patients but also improves their perceived QOL.

References

1. Adler L, Dietrich A, Reimherr F, et al. Safety and tolerability of once versus twice daily atomoxetine in adults with ADHD. *Ann Clin Psychiatry*. 2006;18:107-113.
2. Adler LA, Sutton VK, Moore RJ, et al. Quality of life assessment in adult patients with attention-deficit/hyperactivity disorder treated with atomoxetine. *J Clin Psychopharmacol*. 2006;26:648-652.

Shedding Light on ADHD Symptoms...Literally

A new study suggests that light therapy, during the fall and winter months, may be a useful supplementary treatment for adults with ADHD.¹ Many adults with ADHD have a delayed sleep/activity rhythm, while others are subject to seasonal affective disorder (SAD), a depression subtype that occurs in the fall/winter months. In fact, SAD symptoms are frequently comorbid with adult ADHD.² In both SAD and delayed sleep/activity rhythms, the associated symptoms of fatigue and poor concentration can be especially disabling for adults with ADHD, particularly in the early part of the day. The study showed that participants exposed to 30 minutes of light therapy, using a full-spectrum fluorescent light box that filtered out ultraviolet wavelengths, had a significant decrease in core ADHD symptoms such as inattention, difficulty sustaining effort, impulsive responses to stimuli, and hypo-arousal/fatigue. In this study, 55% of participants had a marked improvement on depression scores and 28% had a full or partial improvement in attention deficit symptoms, measured with both questionnaires and actual laboratory-based tasks. The strongest predictor of improvement in ADHD symptoms resulted from a change in circadian activity rhythms rather than decreasing the symptoms of SAD that are often experienced by adults with ADHD. Many adults with ADHD have a phase delay in their circadian rhythms that causes them to go to bed late and, therefore, makes it more difficult to get up in the morning. The investigators suggest that light therapy during the fall/winter period may correct a core deficit in the basic arousal mechanism in adults with ADHD, and may change circadian rhythms so that they return to a more conventional schedule.

References

1. Rybak YE, McNeely HE, Mackenzie BE, Jain UR, Levitan RD. An open trial of light therapy in adult attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2006;67:1527-1535.
2. Amons PJ, Kooij JJ, Haffmans PM, Hoffman TO, Hoencamp E. Seasonality of mood disorders in adults with lifetime attention-deficit/hyperactivity disorder (ADHD). *J Affect Disord*. 2006;91:251-255.

Undertreated Under-the-Radar Symptoms Can Blunt Stimulant Effects

Nierenberg and associates showed that adults with ADHD have more depression, mania, mixed or cycling bipolar and hypomania than do individuals without ADHD.¹ However, patients with untreated ADHD complain of internalizing symptoms, such as temper outbursts, low self-esteem, anxiety, and poor motivation, which do not meet the diagnostic criteria for a mood or anxiety disorder. A study by Weiss, Hechtman, and colleagues showed that a history of comorbid internalizing disorders may be a predictor of diminished responsiveness of ADHD symptoms to stimulants.² In their randomized, placebo-controlled, prospective trial, 98 adults

with ADHD, half of whom had a history of DSM-IV depression or anxiety, received psychotherapy combined with dextroamphetamine, the SSRI paroxetine, both, or placebo for 20 weeks. Attention deficit/hyperactivity disorder symptoms were significantly lower in those treated with dextroamphetamine ($P=.012$). As anticipated, paroxetine had no effect on ADHD symptoms; ADHD symptoms responded to dextroamphetamine or combined treatment, and mood-related symptoms responded to paroxetine or combined treatment. The interesting component of this study is that patients with a lifetime history of "under-the-radar" internalizing disorders demonstrated a lower response to amphetamine than did patients with no such underlying diagnosis ($P=.04$). Thus, the clinical implications of this study are that physicians need to ask patients about the presence of internalizing symptoms, since such symptoms may not be treatable with stimulants alone and, in fact, can blunt the overall effects of the stimulant. Also, clinicians need to ask patients presenting with affective symptoms about ADHD because, if they are present, ADHD symptoms do not respond to SSRI monotherapy. Even in the absence of an internalizing diagnosis, physicians who prescribe an SSRI in an ADHD patient may see an improvement that may lead them to continue the prescription. More research is needed to investigate the response of ADHD and atypical symptoms in individuals both with and without internalizing problems.

References

1. Nierenberg AA, Miyahara S, Spencer T, et al; STEP-BD Investigators. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol Psychiatry*. 2005;57:1467-1473.
2. Weiss M, Hechtman L; the Adult ADHD Research Group. A randomized double-blind trial of paroxetine and/or dextroamphetamine and problem-focused therapy for attention-deficit/hyperactivity disorder in adults. *J Clin Psychiatry*. 2006;67:611-619.

Posttest

Please select only one answer for each question. Circle the letter corresponding to the correct answer on the answer form on the next page.

- ADHD and restless leg syndrome are linked by which 2 characteristics?
 - Depression and physical pain
 - Sleep disruption and hyperactivity
 - Inattentiveness and muscle spasms
 - Substance abuse disorder and impulsivity
- The most common example of sleep-disordered breathing is:
 - Early/middle insomnia
 - Snoring
 - Obstructive sleep apnea
 - Daytime drowsiness
- Which is not a characteristic of a short-acting stimulant?
 - Limited duration of effect
 - Works quickly, achieving a clinical effect in 20-30 minutes
 - Requires dosing 3-4 times a day
 - None of the above
- Which of the following is not true regarding the use of long-acting stimulants in partial responders to shorter-acting stimulants in ADHD?
 - Extended-release formulations of mixed amphetamine, methylphenidate, and atomoxetine can be used.
 - They can provide symptom relief for 8-14 hours.
 - Atomoxetine can ameliorate ADHD symptoms in once-daily and sometimes twice-daily dosing.
 - A second medication can increase the duration and extent of therapeutic effect for partial responders to monotherapy.
- What is true about the dose-limited side effects of shorter-acting stimulants?
 - Motor tics are the most likely side effect observed.
 - The patient should be removed from all short-acting stimulants if side effects develop.
 - Adding clonidine to the regimen can ameliorate symptoms of irritability but can increase appetite.
 - Atomoxetine can provide relief from the main side effects of OROS-methylphenidate.
- If motor tics emerge as a significant side effect to a short-acting stimulant, it can be combined with:
 - Mixed amphetamine salt
 - Clonidine
 - Serotonin reuptake inhibitor
 - B or C
- Ampakine CX717 is a drug that has what effect on AMPA receptor activity?
 - It increases activity.
 - It decreases activity.
 - It directly antagonizes activity.
 - It indirectly antagonizes activity.
- In the quality of life study by Adler, what is not true about atomoxetine?
 - Its use as a stimulant was approved by the FDA in 2002.
 - It is a selective-norepinephrine reuptake inhibitor.
 - It improved overall mental health.
 - It ameliorated ADHD symptoms.
- Both seasonal affective disorder and delayed sleep/activity rhythms have associated symptoms of:
 - Fatigue and poor concentration
 - Impulsivity and hostility
 - Depression and anxiety
 - Insomnia and night sweats
- Which is an example of an internalizing symptom?
 - Temper outburst
 - Low self-esteem
 - Poor motivation
 - All of the above

Adult ADHD: Issues and Answers

Successful completion of the posttest examination (at least 70% correct) and activity evaluation is required to earn a maximum of .75 AMA PRA Category I Credits™. Statements of Credit will be awarded upon successful completion of the posttest and evaluation.

To receive a certificate of credit, please mail or fax this completed form to:
 Medical Education Resources, Inc.
 Attention: Certificate Processing
 1500 West Canal Court
 Littleton, CO 80120
 Fax: (303)798-5731

Posttest Answer Form	
(Circle the correct answer to each question)	
1. A B C D	6. A B C D
2. A B C D	7. A B C D
3. A B C D	8. A B C D
4. A B C D	9. A B C D
5. A B C D	10. A B C D

There is no fee for certificate processing.

To receive credit, you must answer 7 of the 10 posttest questions correctly, complete all forms, and submit them by November 30, 2007.

Registration for Credit (please print)

First Name: _____

Last Name: _____

Degree: _____

Specialty: _____

Street Address (your certificate will be sent here):

City: _____

State: _____

ZIP: _____

State/License #: _____

Phone: _____ Fax: _____

E-mail: _____

I certify that I have completed this CME activity. The actual amount of time I spent on this activity was ____ minutes.

Signature _____ Date _____

Activity Evaluation Form

Please circle the appropriate rating in answer to the questions that follow:

- How would you rate the content of this CME activity?
 Poor 1 2 3 4 5 Outstanding
- How relevant was the content of this activity to your practice?
 Not relevant at all 1 2 3 4 5 Very relevant
- To what degree were you able to meet each of the learning objectives of the activity? Please respond to each learning objective listed below:
 - Identify common associated sleep disturbances that may affect the diagnosis of ADHD
 Poor 1 2 3 4 5 Outstanding
 - Summarize several treatment strategies that may be necessary to optimize the management of a subject with ADHD
 Poor 1 2 3 4 5 Outstanding
 - Evaluate recent research on the treatment of adult ADHD to advance the treatment and management strategies for adult ADHD
 Poor 1 2 3 4 5 Outstanding
- Based on your knowledge and experiences, the level of the activity was:
 Basic Appropriate Complex
- How would you rate the activity overall?
 Poor 1 2 3 4 5 Outstanding
- Do you believe this activity was fair, balanced, and free of commercial bias?
 - Yes No
 - If No, please state the reason:

 - How much did this activity enforce your current clinical opinions?
 Not at all 1 2 3 4 5 A lot
 - How much new information did you find in this activity?
 None 1 2 3 4 5 A lot
 - As a result of this activity, will you alter your practice?
 Yes No
 - If Yes, please describe any change(s) you plan to make:

 - How committed are you to making these changes?
 Not at all committed 1 2 3 4 5 Very committed
 - If No, why not? _____
- Additional comments about this activity?

- Do you feel future activities on this subject matter are necessary and/or important to your practice?
 Yes No
- Please list any other topics that would be of interest to you for future educational activities.




Adult ADHD: Issues and Answers

The information in this publication does not necessarily reflect the opinions of the publisher or grantor.

© 2006 Medical Education Resources, Inc. All rights reserved.

MLSHAD93



MedLearning Inc.
611 Route 46 West
Hasbrouck Heights, NJ 07604

PRSRT STD
U.S. POSTAGE PAID
RED BANK, NJ
Permit No. 556