

# Adult ADHD: Issues and Answers

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

## Can an Anchovy a Day Keep Impulsivity Away?

Omega-3 essential polyunsaturated fatty acids (EFAs) may be pivotal to certain behaviors and psychiatric conditions, including the impulsivity and aggressiveness associated with adult attention-deficit/hyperactivity disorder (ADHD). Yet, the published data are scant and difficult to interpret. EFAs selectively concentrate in synaptic neuronal membranes and regulate vascular and immune functions that affect the central nervous system.<sup>1</sup> Because they are solely available via dietary sources, notably oily fish like anchovies, sardines, and salmon (see Table 1), insufficient intake theoretically could correlate with certain psychiatric conditions. Much research has been conducted to determine whether EFA supplementation, particularly with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can produce improved psychiatric outcomes. For example, Freeman and colleagues did a meta-analysis on a handful of studies that treated schizophrenic patients with omega-3 EFA or placebo.<sup>2</sup> They found that omega-3 EFA failed to improve symptoms as measured by the Positive and Negative Syndrome Scale (PANSS). They also performed a random effects model, which yielded virtually identical results. The same group also performed a meta-analysis of trials in bipolar and unipolar depression.<sup>2</sup> The studies varied greatly in both design and execution. Not surprisingly, the analysis showed that the results of the studies were highly heterogeneous, indicating that different studies found considerably disparate results. In a dose-finding study of depressed patients being treated with standard antidepressants at recommended doses, a particularly positive effect (as measured by Hamilton Depression Rating Scale, the Montgomery-Asberg Depression Rating Scale, and the Beck Depression Inventory) was seen with EPA 1 g, with lesser efficacy noted at higher doses, indicating a possible ceiling effect.<sup>3</sup>

## Et tu, ADHD?

The EFA studies that involve patients with ADHD and/or its characteristics tend to be inconclusive. One study shows the murder rates are higher in countries with lower seafood consumption,<sup>4</sup> which is consistent with data demonstrating that lower tissue levels of omega-3 EFA predict greater hostility.<sup>5</sup> Currently, only 2 placebo-controlled studies have been published involving adjunctive EFA treatment in ADHD.<sup>6,7</sup> Both studies, which lasted 12 to 16 weeks, failed to show a statistically significant improvement in any objective or subjective measure of ADHD symptoms. Other studies have combined a number of supplements along with DHA/EPA and have obtained improvements in behavior. For example, Stevens and colleagues randomly assigned 50 children with ADHD-type symptoms in a placebo arm and an arm that received DHA/EPA plus arachidonic acid, gamma-linolenic acid, and

**Table 1. Which fish is oily?**

Oily fish	Nonoily fish
Anchovies	Catfish
Eel	Cod
Herring	Flounder
Kipper	Flying fish
Mackerel	Haddock
Salmon	Hake
Sardines	Halibut
Swordfish	Red snapper
Trout	Sea bass
Tuna (fresh only, not canned)*	Sole (lemon and Dover)

\*Tuna only counts as an oily fish when it is fresh. This is because the canning process reduces the omega-3 EFA to concentration levels similar to those of nonoily white fish.

vitamin E.<sup>8</sup> After 4 months, improvements in teacher-rated attention and parent-rated conduct were observed, as well as a reduction in the proportion of children whose behavior fulfilled clinical criteria for oppositional defiant disorder. But which supplement provided the greater benefit? The design of the study obscures the answer.

## Should research continue?

Yes. The evidence is enticing and the potential clinical benefit is significant, particularly in light of the apparent safety and tolerability of omega-3 EFA. However, much work needs to be done, beginning with setting up properly designed studies. Studies need to address many questions, eg, how long should a study last? Tissue composite studies show that the time frame for dietary intake and subsequent EFA changes in tissues varies. As shown by animal studies of depletion and repletion of EFAs, serum and liver concentrations can rebound within 2 weeks, while tissues such as the brain require 12 weeks for DHA composition to be stored.<sup>2</sup> Levels of omega-3 EFA in human adipose tissue reflect dietary intake periods of 2 or 3 years.<sup>9</sup> Studies will need to determine which psychiatric disorders may actually benefit from omega-3 EFA. Dose-ranging studies would be needed. Comparisons of

## Statement of Need

Attention-deficit/hyperactivity disorder (ADHD) is widely held as a disorder of children and adolescents. However, in more than half of those diagnosed with childhood ADHD, the disorder persists into adulthood, and, in many cases, the initial clinical presentation of ADHD occurs in adulthood. Accurate diagnosis of ADHD may be difficult in adults, as patients often present with a complex of nonspecific heterogeneous symptoms and functional disturbances, such as problems with sleep and working memory. Further, comorbid psychiatric and personality disorders often complicate diagnosis and have fostered the development of new diagnostic tools for adult ADHD. In the treatment of adult ADHD, stimulants, specific reuptake inhibitors, and more recently, chirally pure and extended-release preparations, have proven to be useful pharmacologic options; however, alternative and complementary interventions, such as nutritional supplementation and neurofeedback, have received recent attention as nonpharmacologic treatment modalities. The diagnosis and treatment of adult ADHD continue to pose unique challenges to clinicians, in part due to the heterogeneity of the disorder and the coexistence of disorders with overlapping symptoms. Current therapeutic approaches have provided favorable, although variable, outcomes in the management of the core symptoms of inattention, hyperactivity, and impulsivity. This newsletter will explore recent and ongoing efforts to refine the diagnosis and treatment of ADHD and its associated comorbidities.

## References

1. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. *Ambul Pediatr.* 2007;7(1Suppl):73-81.
2. Donnelly CL, Reinherz FW, Young JL. Differential diagnosis and treatment of adult ADHD and neighboring disorders. *CNS Spectr.* 2006;11(10 Suppl 11):1-14.
3. Philipsen A. Differential diagnosis and comorbidity of attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) in adults. *Eur Arch Psychiatry Clin Neurosci.* 2006;256(Suppl 1):42-46.
4. 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.

## Learning Objectives

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

- Discuss the evidence supporting the potential benefits of neurofeedback and essential fatty acid supplementation in the treatment of adult ADHD
- Identify the specific aspects of working memory and sleep behavior as they pertain to subgroups of adults with ADHD
- Evaluate recent research on the mechanism of action, advantages, and disadvantages of chirally pure and extended-release ADHD therapies
- Summarize common challenges to the accurate diagnosis of ADHD in adults and recent advances in diagnostic tools

## 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: April 2007  
Expires: March 31, 2008

## 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 © 2007 Medical Education Resources, Inc. All rights reserved.

EPA and DHA would elucidate the differential, collective, and even synergistic effects of these 2 pivotal omega-3 EFAs. Studies need to address questions of how EFA in the brain can be measured peripherally, whether decreased EFA in the blood results only from dietary deficiency or whether there is a yet unidentified metabolic aberration at play, whether the psychiatric disorder or the lack of dietary omega-3 comes first, and whether there is an inborn error of metabolism that is exacerbated when combined with a lack of dietary omega-3 EFA.

Omega-3 EFAs have potential antiatherogenic, antithrombotic, and antiarrhythmic properties, but their role in psychiatry remains controversial and short on clinical data. Certainly, patients with psychiatric disorders should not opt for EFA supplementation in place of established treatment modalities. Yet, omega-3 EFA might provide some important health benefits to patients with psychiatric disorders, particularly in light of the high prevalence of smoking and obesity in such patients, and the metabolic side effects (eg, hyperglycemia, hypertriglyceridemia) of some psychotropic medications.

## References

1. Salem N Jr, Litman B, Kim HY, Gawrisch K. Mechanisms of action of docosahexaenoic acid in the nervous system. *Lipids.* 2001;36:945-959.
2. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry.* 2006;67:1954-1967.
3. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry.* 2002;59:913-919.
4. Hibbeln JR. Seafood consumption and homicide mortality. A cross-national ecological analysis. *World Rev Nutr Diet.* 2001;88:41-46.
5. Iribarren C, Markovitz JH, Jacobs DR Jr, Schreiner PJ, Daviglius M, Hibbeln JR. Dietary intake of n-3, n-6 fatty acids and fish: relationship with hostility in young adults – the CARDIA study. *Eur J Clin Nutr.* 2004;58:24-31.
6. Bekaroglu M, Aslan Y, Gedik Y, et al. Relationships between serum free fatty acids and zinc, and attention deficit hyperactivity disorder: a research note. *J Child Psychol Psychiatry.* 1996;37:225-227.
7. Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *J Pediatr.* 2001;139:189-196.
8. Stevens L, Zhang W, Peck L, et al. EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. *Lipids.* 2003;38:1007-1021.
9. Guallar E, Aro A, Jimenez FJ, et al. Omega-3 fatty acids in adipose tissue and risk of myocardial infarction: the EURAMIC study. *Arterioscler Thromb Vasc Biol.* 1999;19:1111-1118.

## Neurofeedback: A drug-free alternative?

Neurofeedback (NFB), sometimes called neurobiofeedback or EEG (electroencephalogram) biofeedback, is a method of attempting to train brain wave activity, as measured by electrodes on the scalp, and is presented to an individual as feedback in the form of a video display, sound, or vibration. If brain activity changes in the direction desired by the therapist, a positive reward feedback is given to the individual, and if it regresses, either a negative feedback or no feedback is given, depending on the protocol. The utility of NFB in ADHD is controversial and remains an area of active research. Some reviewers have commented that NFB is considered the only treatment modality in complementary medicine to demonstrate improvement in ADHD symptoms in the absence of stimulant therapy.<sup>1</sup> Functional neuroimaging studies carried out in individuals with ADHD have shown abnormal functioning of the anterior cingulate cortex (ACC) during tasks involving selective attention.<sup>2</sup> Levesque and coworkers recently conducted a study on stimulant-free children with ADHD in which functional magnetic resonance imaging (fMRI) was used to

measure the effect of NFB training on the neural substrates of selective attention in children with ADHD.<sup>3</sup> Participants from both the NFB groups and placebo groups were scanned 1 week prior to NFB (Time 1) and 1 week after the end of this training (Time 2), while they performed a Counting Stroop task (CST). At Time 1 for both groups, the CST was associated with significant loci of activation in the left superior parietal lobule. No activation was noted in the ACC. At Time 2 for both groups, the CST was still associated with significant activation of the left superior parietal lobule. This time, however, the NFB group demonstrated a significant activation of the right ACC. These results suggest that in ADHD children, NFB training has the capacity to normalize the functioning of the ACC, the key neural substrate of selective attention.

NFB has its constraints. A sustained, long-term improvement may necessitate as many as 60 sessions or 6 months of treatment. Significant controversy remains over:

1. Standardizing the methodology of NFB
2. Determining the appropriate control treatment in clinical trials
3. Generalizability of the improvement, ie, whether the improvement persists after the discontinuation of NFB<sup>4</sup>

#### References

1. Fox DJ, Tharp DF, Fox LC. Neurofeedback: an alternative and efficacious treatment for attention deficit hyperactivity disorder. *Appl Psychophysiol Biofeedback*. 2005;30:365-373.
2. Bush G, Frazier JA, Rauch SL, et al. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. *Biol Psychiatry*. 1999;45:1542-1552.
3. Levesque J, Beauguard M, Mensour B. Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. *Neurosci Lett*. 2006;394:216-221.
4. Loo SK, Barkley RA. Clinical utility of EEG in attention deficit hyperactivity disorder. *Appl Neuropsychol*. 2005;12:64-76.

#### Case study

The patient is a female, 30-year-old interior designer with a lifelong history of difficulty paying attention. Her medical history reveals these other symptoms:

- Organizational difficulties
- Trouble planning
- Procrastination
- Forgetfulness (eg, she misses appointments)
- Regularly misplaces her planner and phone
- Trouble completing tasks
- Although very creative, she runs late on projects for clients
- Has failed to pay last year's taxes because of disorganization
- Office is messy; cannot find things
- Poor driver (has had several infractions)

A review of childhood symptoms reveals that her third-grade teacher observed that she did her homework but often left it home. Her mother reports that throughout childhood, her room was a mess. The patient often feels overwhelmed when she is behind on projects, runs up against deadlines, and misplaces things. She is frequently anxious in these circumstances, but no formal symptoms indicate anxiety disorder, major depression, or bipolar disorder.

She was diagnosed with inattentive ADHD; treatment was initiated with OROS methylphenidate at a dose titrated up to 54 mg/d. This resulted in significant improvement in attention, reduced distraction, and fewer incidents of misplaced things. However, she still habitually ran late on projects and had trouble planning, which led her to be moody and intermittently overwhelmed. She started cognitive behavior therapy and EFA supplementation and felt improvement in her moodiness and her ability to complete tasks. Although she continues EFA supplementation, it is not clear whether her improvement is due to the EFA or to the effects of the cognitive behavior therapy.

#### ADHD questionnaires: Sometimes shorter is better

Questionnaires intended to assess behavioral concomitants of executive function deficits (EFDs) may be useful in identifying adults with ADHD who show functional impairments. Using the Current Behavior Scale (CBS), a 99-item questionnaire developed by Barkley in 1997, a study by Biederman and colleagues, currently in press, documented that ADHD individuals with high scores on this scale had reduced social class, educational and occupational attainments, and impairments in adaptive social and leisure functioning compared to subjects with ADHD who had low scores.<sup>1</sup> Although these findings suggested that the CBS is useful in making a diagnosis of ADHD, its current version is cumbersome for clinical use. Thus, Biederman et al aimed to abbreviate the CBS to a smaller subset and to assess its usefulness compared to the larger CBS.<sup>2</sup> There were 200 adult participants with ADHD enrolled in a family study of adult ADHD. Factor analysis was used to reduce the number of items in the 99-item CBS. The shorter scale, as presented in Table 2, reflects the factor solution that provided 8 items with factor loadings above 0.70. This abbreviated set of items was highly correlated with the 99-item CBS (0.91) and was similarly related to functional outcomes compared to the 99-item CBS (average correlation of 0.30 vs 0.32). These results show that a smaller set of 8 empirically derived items measuring behavioral manifestations of EFD can help identify a sizable number of adults with ADHD at high risk for functional deficits in educational, occupational, and interpersonal functioning.

#### References

1. Biederman J, Petty C, Fried R, et al. Can self-reported behavioral scales assess executive function deficits? A controlled study of adults with ADHD. *J Nervous Mental Dis*. 2007 (in press).
2. Biederman J, Petty CR, Fried R, et al. Utility of an abbreviated questionnaire to identify individuals with ADHD at risk for functional impairments. *J Psychiatr Res*. 2007 (in press).

**Table 2. Current Behavior Scale (CBS) items with a factor loading\* above 0.700<sup>2</sup>**

Item	Factor loading
Have trouble planning ahead or preparing for upcoming events	0.712
Can't seem to accomplish goals I set for myself	0.704
Can't seem to hold in mind things I need to remember to do	0.722
Easily frustrated	0.712
Have difficulty motivating myself to stick with my work and get it done	0.720
Have trouble doing what I tell myself to do	0.746
Lack self-discipline	0.718
Have trouble organizing my thoughts	0.704

\* A Pearson correlation between a variable and a factor.

## Journal reviews

### Chirally pure methylphenidate isomer efficacious in adult population

Racemic methylphenidate (r-MPH), while FDA approved for children with ADHD, is not yet approved as a treatment for adult ADHD. Studies suggest the therapeutic effects of r-MPH are mediated primarily by blocking the presynaptic dopamine transporter, thereby raising levels of dopamine in the synaptic cleft. Inhibition of dopamine reuptake is accomplished almost exclusively by the *d-threo* enantiomer of MPH,<sup>1</sup> now available as the chirally pure isomer dexmethylphenidate (*d*-MPH). In preclinical studies, *d*-MPH raised extracellular levels of dopamine more than 6-fold while *l-threo* MPH (*l*-MPH) had no effect.<sup>1</sup> In addition, *d*-MPH binds specifically to dopamine transporters primarily in the basal ganglia, whereas *l*-MPH binding is largely nonspecific. A multicenter, randomized, fixed-dose, double-blind, placebo-controlled study performed by Spencer and the Adult ADHD Research Group evaluated the efficacy of extended-release dexmethylphenidate (*d*-MPH-ER) in adults with ADHD.<sup>2</sup> In this study, adults with ADHD were randomized to receive once-daily *d*-MPH-ER 20 mg, 30 mg, or 40 mg or placebo for 5 weeks. The primary efficacy variable was change from baseline to final visit in *DSM-IV* ADHD Rating Scale (ADHD-RS) total score. Secondary efficacy parameters included the proportion of patients with improvement  $\geq 30\%$  in ADHD-RS total score and final scores on the Clinical Global Impressions-Improvement (CGI-I) scale. Of 218 evaluable patients, 184 (84%) completed the study. All *d*-MPH-ER doses were significantly superior to placebo in improving ADHD-RS total scores. Placebo scores improved by 7.9; *d*-MPH-ER, 20 mg, improved by 13.7 ( $P=.006$ ); *d*-MPH-ER, 30 mg, improved by 13.4 ( $P=.012$ ); and *d*-MPH-ER, 40 mg, improved by 16.9 ( $P<.001$ ). Overall distribution of CGI-I ratings at final visit was significantly better with each *d*-MPH-ER dosage than with placebo. The most commonly reported

treatment-related adverse events—headache, decreased appetite, dry mouth, insomnia, and jitteriness—were consistent with the known safety profile of r-MPH and *d*-MPH. This study demonstrated that once-daily *d*-MPH-ER at 20 mg, 30 mg, or 40 mg is a safe and effective treatment for adults with ADHD.

### Working memory deficits in adults with ADHD—gender may be more significant than subtype differences

Working memory performance is important for maintaining functioning in cognitive, academic, and social activities. Previous research suggests that prevalent working memory deficits exist in children with ADHD. There is a growing body of literature that characterizes working memory functioning according to ADHD subtypes in children.<sup>3,4</sup> However, the expression of working memory deficits in adults with ADHD and how they vary according to subtype is less well documented. To fill that gap in knowledge, Schweitzer and colleagues assessed differences in working memory functioning between normal control (NC) adults (n=18); patients with ADHD, combined type (ADHD-CT; n=17), and ADHD, inattentive type (ADHD-IA; n=16) using subtests from the Wechsler Adult Intelligence Scale-III and Wechsler Memory Scale-III and the Paced Auditory Serial Addition Task (PASAT).<sup>5</sup> The results showed that ADHD groups displayed significant weaknesses in contrast to the NC group on working memory tests requiring rapid processing and active stimulus manipulation. This included the Letter-Number-Sequencing test of the Wechsler scales, PASAT omission errors, and the longest sequence of consecutive correct answers on the PASAT. No overall ADHD group subtype differences emerged. Yet, differences between the ADHD groups and the NC group varied depending on the measure and the gender of the participants. Gender differences in performance were evident on some measures of working memory, regardless of group, with males performing better than females. Overall, these data support a dimensional interpretation of working memory deficits experienced by the ADHD-CT and ADHD-IA subtypes, rather than an absolute difference between subtypes. Future studies should test the effects of processing speed and load on subtype performance and how those variables interact with gender in adults with ADHD.

### Study of college students shows an ADHD-sleep disorder link

The literature is replete with reports of childhood and adolescent ADHD-associated sleep problems, including longer sleep duration, dyssomnia, restless sleep, periodic leg movement (PLM), snoring, and other sleep-disordered breathing (SDB) problems.<sup>6-8</sup> Among these, the most confirmatory associations of ADHD are with PLM,<sup>7</sup> and, to a lesser degree, SDB.<sup>6</sup> Longitudinal research has confirmed that snoring in children predicts the subsequent onset of hyperactivity.<sup>8</sup> In comparison, no longitudinal research has, thus far, investigated whether ADHD predicts the subsequent onset of sleep problems. There has been a scarcity of adequate data delineating the associations of ADHD with other sleep problems among adults. In light of this, and given the considerable public health importance of adult ADHD, Gau et al conducted a survey study of 2284 college students to examine whether the associations of ADHD symptoms with sleep problems are similar to those found among children.<sup>9</sup> Each student completed a questionnaire regarding sleep schedule (self-estimated total sleep duration and sleep need), sleep problems (dyssomnia, parasomnia, and snoring), and the Chinese version of the Adult ADHD Self-Report Scale (AASRS). Subjects were grouped separately for the inattention and hyperactivity subscales into “highly likely ADHD” (2.3%, 0.7%), “probable ADHD” (21.3%, 5.7%), and “probably non-ADHD” (76.4%, 93.6%) subsets, according to the scoring scheme of the AASRS subscales. The results

showed that, for both inattention and hyperactivity symptoms, the highly likely ADHD and probable ADHD groups were more likely than the non-ADHD group to have a variety of current and lifetime sleep problems. No significant difference in sleep problems was observed between the highly likely ADHD and probable ADHD groups. Inattention, but not hyperactivity, was associated with greater sleep need and greater difference between sleep need and self-estimated nocturnal sleep duration. Hyperactivity, but not inattention, was associated with decreased nocturnal sleep duration. Thus, consistent with prior findings from children and adolescents, ADHD symptoms in young adults are related to sleep problems. Further studies on adults with ADHD should help to refine an understanding of the causal basis for any implications of this association.

### OROS MPH useful for adult ADHD with emotional/oppositional symptoms

For most drug products, the oral route remains the most predominant and acceptable form of administration. However, certain molecules may have low oral bioavailability because of solubility and permeability limitations. To overcome these obstacles, controlled- or modified-release products are increasingly being developed. One such product, used in a variety of drug classes for diseases as diverse as epilepsy, hypertension, ADHD, and diabetes, uses the principle of osmosis to deliver drugs from the oral dosage form in a controlled manner, typically in a zero-order profile.

Osmotic release oral system (OROS) methylphenidate (MPH) is a long-acting stimulant demonstrated to be effective in the treatment of children,<sup>10</sup> adolescents,<sup>11</sup> and adults<sup>12</sup> with ADHD. Reimherr and colleagues performed a double-blind, placebo-controlled, crossover study of OROS MPH in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder.<sup>13</sup> Subjects met both *DSM-IV-TR* and Utah Criteria for ADHD in adults. Outcome measures included the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDs), the adult ADHD-Rating Scale (ADHD-RS), and the Clinical Global Impressions-Improvement scale (CGI-I). At baseline, subjects were categorized as having significant emotional symptoms with the WRAADDs and/or significant oppositional-defiant symptoms using a self-report scale assessing the *DSM-IV* criteria for oppositional defiant disorder. Each double-blind arm lasted 4 weeks. The results showed that 17% of the sample (n=8) had ADHD alone, 38% (n=18) had ADHD plus significant emotional symptoms, and 40% (n=19) had ADHD with both significant emotional and oppositional symptoms. At a mean 0.75 mg/kg, OROS MPH was superior to placebo for all clinical measures (total WRAADDs score decreased 42% vs 13%, respectively;  $P<.001$  and total ADHD-RS score decreased 41% vs 14%, respectively;  $P=.003$ ; as well as improvement in the subscales addressing inattention, hyperactivity/impulsivity, and emotional dysregulation. Thus, OROS MPH was demonstrated to be effective in treating adult ADHD. In this study, ADHD alone was relatively uncommon, with over 80% of participants having a combination of ADHD and emotional and/or oppositional symptoms.

### MAS XR therapy found to be safe, effective over long-term use

A study by Spencer and colleagues has shown that mixed amphetamine salts extended-release (MAS XR) therapy controls ADHD symptoms and has an excellent safety profile over long-term use.<sup>14</sup> In this study, the efficacy of MAS XR (10–60 mg/d) in 138 adolescents with ADHD (mean age, 14.4 years; 71% male) was assessed in a 6-month, open-label, extension study following participation in a 4-week, randomized, placebo-controlled trial of MAS XR. Study subjects exhibited sustained improvement in ADHD symptoms: end-point

ADHD-RS-IV total score was significantly decreased from baseline ( $-7.9$ ;  $P<.001$ ); similar decreases were seen for hyperactivity/impulsivity ( $-4.0$ ;  $P<.001$ ) and inattentiveness ( $-3.8$ ;  $P<.001$ ). Based on CGI-I ratings, 61% of patients were very much/much improved, 33% were unchanged, 6% were much worse, and 0% were very much worse. The most common adverse events related to MAS XR were anorexia (25%), weight loss (25%), headache (15%), and nervousness (13%). The incidence of reported adverse events appeared to be dose dependent: the incidence was lowest among patients receiving MAS XR 10 mg (25%), and highest in those receiving MAS XR 30 mg (70%), 40 mg (67%), 50 mg (67%), and 60 mg (75%). Future studies may assess the safety and tolerability of MAS XR over periods longer than 6 months, which may provide results that differ from the pattern of results described in this study.

### References

1. Ding YS, Fowler JS, Volkow ND, et al. Chiral drugs: Comparison of the pharmacokinetics of [11C]d-threo and l-threo-methylphenidate in the human and baboon brain. *Psychopharmacology (Berl)*. 1997;131:71–78.
2. Spencer TJ, Adler LA, McGough JJ, Muniz R, Jiang H, Pestreich L, Adult ADHD Research Group. Efficacy and safety of dexamethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2006; November 28 [Epub ahead of print].
3. Houghton S, Douglas G, West J, et al. Differential patterns of executive function in children with attention-deficit hyperactivity disorder according to gender and subtype. *J Child Neurol*. 1999;14:801–805.
4. Schmitz M, Cadore L, Paczko M, et al. Neuropsychological performance in DSM-IV ADHD subtypes: an exploratory study with untreated adolescents. *Can J Psychiatry*. 2002;47:863–869.
5. Schweitzer JB, Hanford RB, Medoff DR. Working memory deficits in adults with ADHD: is there evidence for subtype differences? *Behav Brain Funct*. 2006;2:43.
6. Chervin RD, Archbold KH, Dillon JE, et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. *Pediatrics*. 2002;109:449–456.
7. Crabtree VM, Ivanenko A, Gozal D. Clinical and parental assessment of sleep in children with attention-deficit/hyperactivity disorder referred to a pediatric sleep medicine center. *Clin Pediatr*. 2003;42:807–813.
8. Chervin RD, Ruzicka DL, Archbold KH, Dillon JE. Snoring predicts hyperactivity four years later. *Sleep*. 2005;28:885–890.
9. Gau SS, Kessler RC, Tseng WL, et al. Association between sleep problems and symptoms of attention-deficit/hyperactivity disorder in young adults. *Sleep*. 2007;30:195–201.
10. Wolraich ML, Greenhill LL, Pelham W, et al. Randomized, controlled trial of oros methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 2001;108:883–892.
11. Biederman J, Mick E, Surman C, et al. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2006;59:829–835.
12. McGough JJ, McBurnett K, Bukstein O, Wilens TE, Greenhill L, Lerner M, Stein M. Once-daily OROS methylphenidate is safe and well tolerated in adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2006;16:351–356.
13. Reimherr FW, Williams ED, Strong RE, Mestas R, Soni P, Marchant BK. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. *J Clin Psychiatry*. 2007;68:93–101.
14. Spencer TJ, Biederman J, Wilens TE. Efficacy and tolerability of long-term, open-label, mixed amphetamine salts extended release in adolescents with ADHD. *CNS Spectr*. 2005;10(10 Suppl 15):14–21.

## Posttest

Please select only 1 answer for each question. Circle the letter corresponding to the correct answer on the answer form on the next page.

1. What can be said about studies involving essential fatty acids (EFAs) in the ADHD population?
  - A. They have failed to show a statistically significant improvement in objective measures of ADHD symptoms
  - B. They have failed to show a statistically significant improvement in subjective measures of ADHD symptoms
  - C. They combine EFAs with other supplements, making it difficult to discern any benefits of the EFAs
  - D. All of the above
2. Turnover in levels of omega-3 EFA varies by tissue type; which human tissue reflects long-term EFA levels?
  - A. Serum
  - B. Adipose
  - C. Liver
  - D. Brain
3. Omega-3 EFA potentially has which type of effect?
  - A. Anticonvulsive
  - B. Antihistaminic
  - C. Antithrombotic
  - D. Antiangiogenic
4. Which of the following foods is not considered an oily fish?
  - A. Eel
  - B. Canned tuna
  - C. Sardines
  - D. Salmon
5. Which alternative medicine is considered the only treatment modality with improvement of central ADHD symptoms in the absence of stimulant therapy?
  - A. Acupuncture
  - B. Biofeedback
  - C. Hypnotherapy
  - D. Rolfing
6. Functional neuroimaging studies carried out in individuals with ADHD have shown abnormal functioning of which area of the brain during tasks involving selective attention?
  - A. Anterior cingulate cortex
  - B. Thalamus
  - C. Hippocampus
  - D. Occipital lobe
7. What can be said about neurofeedback (NFB) compared to stimulant therapy in ADHD?
  - A. NFB is less expensive than stimulant therapy
  - B. NFB does not work as well in ADHD as stimulant therapy
  - C. NFB can require many sessions to invoke successful long-term change
  - D. Successful long-term change can occur in about 30% of ADHD cases after 3 or 4 NFB sessions
8. Which of the following factors is not part of the abbreviated Current Behavior Scale devised by Biederman and colleagues to make it more flexible for clinical use?
  - A. Easily frustrated
  - B. Trouble following the rules in a situation
  - C. Have difficulty motivating myself to stick with my work and get it done
  - D. Can't seem to hold in mind things I need to remember to do
9. What is true about the chirally pure isomer dexamethylphenidate (*d*-MPH)?
  - A. *d*-MPH binds specifically to dopamine transporters primarily in the basal ganglia
  - B. *d*-MPH can lower extracellular levels of dopamine more than 6-fold
  - C. Studies involving *d*-MPH in adult ADHD patients failed to show a significant improvement in ADHD-RS scores
  - D. All of the above
10. Among reports of childhood and adolescent ADHD-associated sleep problems, which sleep problem has the most conformed association with ADHD?
  - A. Snoring
  - B. Sleep-disordered breathing
  - C. Longer sleep durations
  - D. Periodic leg movement

## 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

There is no fee for certificate processing.

### 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 |

To receive credit, you must answer 7 of the 10 posttest questions correctly, complete all forms, and submit them by March 31, 2008.

### 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:
    - Discuss the evidence supporting the potential benefits of neurofeedback and essential fatty acid supplementation in the treatment of adult ADHD  
 Poor 1 2 3 4 5 Outstanding
    - Identify the specific aspects of working memory and sleep behavior as they pertain to subgroups of adults with ADHD  
 Poor 1 2 3 4 5 Outstanding
    - Evaluate recent research on the mechanism of action, advantages, and disadvantages of chirally pure and extended-release ADHD therapies  
 Poor 1 2 3 4 5 Outstanding
    - Summarize common challenges to the accurate diagnosis of ADHD in adults and recent advances in diagnostic tools  
 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? \_\_\_\_\_
7. Additional comments about this activity?  
 \_\_\_\_\_  
 \_\_\_\_\_
8. Do you feel future activities on this subject matter are necessary and/or important to your practice?  
 Yes No
9. 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.**

© 2007 Medical Education Resources, Inc. All rights reserved.

MLSHAD93



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