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CME PSYCHCAST™

BEST PRACTICES IN ADULT ADHD: NEUROBIOLOGY, PHARMACOLOGY, AND EMERGING TREATMENTS

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CME 1.5

ABSTRACT

Treatment of attention-deficit/hyperactivity disorder (ADHD) may positively impact the neurobiology of adult patients with ADHD. Treatment may also minimize impairment from core symptoms and may alter the course of co-morbid disorders such as depression and substance use disorder. However, much of the information on stimulant use in adult ADHD comes from studies conducted in children, and it remains unclear whether there is a difference between children and adults when it comes to the side effects and tolerability of ADHD treatments. It is known that clinical presentation differs between adults and children, with adults demonstrating a higher percentage of mood disorders. Current treatments for adult ADHD include psychosocial therapies and pharmacologic therapies, the latter of which include the stimulants d-methylphenidate extended release (XR), OROS methylphenidate, lisdexamfetamine, and mixed amphetamine salts XR; and the nonstimulant atomoxetine, a selective norepinephrine reuptake inhibitor. There is need for additional study of treatment strategies for adult ADHD. Although all classes of ADHD medications are approved in adults, there are fewer approved formulations for adults than for children. Efficacy in adults is more subjective than in children, which may affect how efficacy rates for adult treatments are calculated. Adults also present a greater diversion risk than children. In addition, there are several new and emerging medication treatments worth considering.

This Expert Roundtable PsychCast™ represents part 2 of a 3-part PsychCast™ series on adult ADHD led by Lenard A. Adler, MD. In this activity, Thomas J. Spencer, MD, discusses the neurobiology and genetics of adult ADHD; Mark A. Stein, PhD, discusses stimulant therapy; and Jeffrey H. Newcorn, MD, reviews nonstimulants and psychosocial treatments.

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CME Course Director

This activity has been peer reviewed and approved by Eric Hollander, MD, Chair and Professor of Psychiatry at the Mount Sinai School of Medicine. Review Date: August 27, 2008.

Faculty Affiliations

Lenard A. Adler, MD, is associate professor of psychiatry and child and adolescent psychiatry, and director of the Adult ADHD Program, both at the New York University Langone School of Medicine. Jeffrey H. Newcorn, MD, is associate professor in the Department of Psychiatry at the Mount Sinai School of Medicine in New York City. Thomas J. Spencer, MD, is associate professor of psychiatry at Harvard Medical School and associate director of the Clinical and Research Program in Pediatric Psychopharmacology at Massachusetts General Hospital in Boston. Mark A. Stein, PhD, is professor in the Department of Psychiatry a the University of Illinois in Chicago and director of the Adult ADHD Clinic.

Faculty Disclosure Policy Statement

It is the policy of the Mount Sinai School of Medicine to ensure objectivity, balance, independence, transparency, and scientific rigor in all CME-sponsored educational activities. All faculty participating in the planning or implementation of a sponsored activity are expected to disclose to the audience any relevant financial relationships and to assist in resolving any conflict of interest that may arise from the relationship. Presenters must also make a meaningful disclosure to the audience of their discussions of unlabeled or unapproved drugs or devices. This information will be available as part of the course material.

Faculty Disclosures

Dr. Adler is a consultant to and on the advisory boards of Abbott, Cephalon, Cortex, Eli Lilly, Novartis, Ortho-McNeil, Janssen, Johnson and Johnson, Merck, New River, Organon, Pfizer, Psychogenics, sanofi-aventis, and Shire; is on the speaker's bureaus of Eli Lilly and Shire; and receives grant/research support from Abbott, Bristol-Myers Squibb, Cephalon, Cortex, Eli Lilly, Janssen, Johnson and Johnson, Merck, National Institute of Drug Abuse, New River, Novartis, Ortho-McNeil, Pfizer, and Shire. Dr. Adler mentions the following experimental/off-label medications for adult ADHD: bupropion and modafinil.

Dr. Newcorn is a consultant to Abbott, Biobehavioral Diagnostics, Eli Lilly, Lupin, Novartis, Ortho-McNeil, Psychogenics, sanofi-aventis, and Shire; and receives research support from Eli Lilly and Ortho-McNeil. Dr. Newcorn mentions the following experimental/off-label medications for adult ADHD: bupropion, clonidine, guanfacine, modafinil, tricyclic antidepressants, and venlafaxine.

Dr. Spencer is a speaker for Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Ortho-McNeil, and Shire; is on the advisory boards of Cephalon, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Ortho-McNeil, Pfizer, and Shire; and receives research support from Cephalon, Eli Lilly, GlaxoSmithKline, Janssen, National Institute of Mental Health, Novartis, Ortho-McNeil, Pfizer, and Shire.

Dr. Stein is a consultant/advisor to Abbott, Novartis, and Pfizer; is a speaker for Novartis and Ortho-McNeil; and receives research support from Eli Lilly, National Institute of Mental Health, Organon, Ortho-McNeil, and Pfizer.

Peer Reviewer

Eric Hollander, MD, reports no affiliation with or financial interest in any organization that may pose a conflict of interest.

Learning Objectives

- Review the neurobiology of attention-deficit/hyperactivity disorder (ADHD), including genetic influences and neuroanatomical and neurochemical factors.
- Describe the current practices and controversies surrounding stimulant therapy in adults with ADHD.
- Discuss the benefits of nonstimulant treatment, psychosocial treatment, and emerging treatment options for adult ADHD.

Statement of Need and Purpose

There are numerous reasons to treat attention-deficit/hyperactivity disorder (ADHD) in adults, including to minimize impairment from core symptoms, to alter the course of co-morbid disorders, and to prevent neurologic deterioration. Untreated adolescents with ADHD show smaller cerebral volumes compared to medicated patients, who more closely resemble healthy controls. However, treatment of adult ADHD is often based on upwardly extended models of child and adolescent care. Adults' differing patterns of co-morbidity and symptom heterogeneity pose new treatment challenges. Having a large number of therapeutic options available for treating ADHD represents an opportunity for patients to achieve better outcomes, but it also raises a challenge for the busy clinician who must choose among many diverse options to tailor a regimen for each individual patient.Psychostimulants remain a viable first-choice strategy, yet there are idiosyncratic differences in response to the various formulations. Recent developments have made stimulants more effective in a range of clinical situations through the development of new release and pharmacokinetic technologies. Distinctions can be made among the long-acting medications with regard to the onset, magnitude, and duration of clinical effects. Recognition of these differences is important for individualizing patient treatment. Transdermal formulations offer new treatment delivery methods that may increase compliance and safety. In addition, a norepinephrine reuptake inhibitor was recently approved for ADHD, adding a new mechanism to the armamentarium. Other nonstimulants, such as venlafaxine, bupropion, and tricyclic antidepressants, have also been used to treat ADHD. While medications are considered the primary treatment for adults with ADHD, several psychosocial treatments seem to be helpful, including cognitive-behavioral therapy, psychoeducation, and organizational and time management training.

Target Audience: psychiatrists, primary care physicians

Accreditation Statement

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

The Mount Sinai School of Medicine designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

To Receive Credit for this Activity

Listen to the Expert Roundtable PsychCast™, reflect on the information presented, and complete the CME posttest and evaluation. To obtain credit, you should score 70% or better. Early submission of this posttest is encouraged. Please submit this posttest by October 1, 2010 to be eligible for credit.

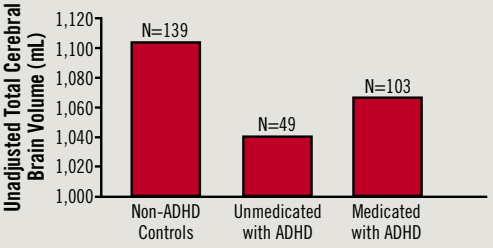
NEUROBIOLOGY, PHARMACOLOGY, AND EMERGING TREATMENT

By Lenard A. Adler, MD

SLIDE LIBRARY

SLIDE 1

Unadjusted Total Cerebral Brain Volume for Unmedicated and Medicated Children and Adolescents with ADHD and Controls[1]



10-year NIMH Study, subjects age 5-18 years at baseline

**P*=.001 by 2-way ANOVA (group [medicated vs. unmedicated vs. control] by sex).

SLIDE 2

Why Treat ADHD in Adults?

Minimize impairment from core symptoms: treat impact of symptoms, not symptoms themselves (eg, occupational problems related to attention, time management; relationship problems, self-esteem)

Alter course of other disorders: treat symptoms commonly associated with personality disorders; treat depressive, anxiety, and substance use disorders

No evidence-based psychosocial treatment, but several interventions have face validity: psychoeducation, CBT, organizational and time-management training

Reference

1. Castellanos FX, Lee PP, Sharp W, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA*. 2002;288(14):1740-1748.

NEUROBIOLOGY AND GENETICS OF ADHD IN ADULTS

By Thomas J. Spencer, MD

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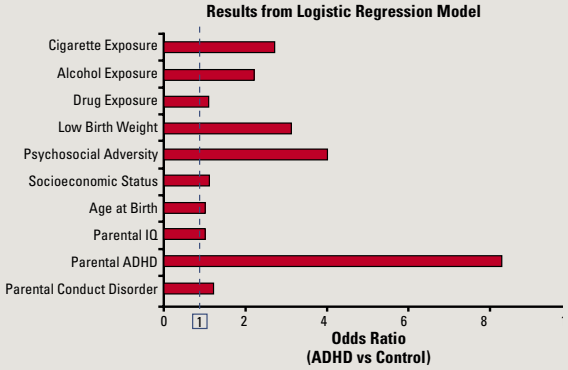
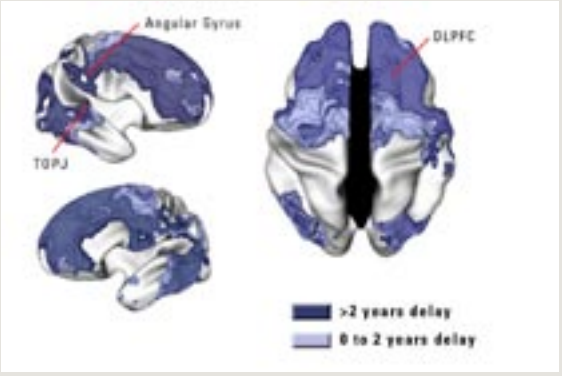
SLIDE 1

Pre- and Perinatal Risk Factors for ADHD



SLIDE 2

ADHD is Characterized By a Delay in Cortical Maturation



DLPFC=dorsolateral prefrontal cortex; TOPJ=temporal-occipital-parietal junction.

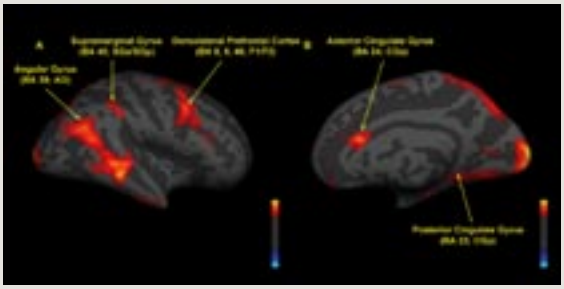
Shaw P, Eckstrand K, Sharp W, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci U S A.* 2007;104(49):19649-19654. Reprinted with permission from *Proceedings of the National Academy of Sciences*, (Copyright 2007). All rights reserved.

References

1. Sonuga-Barke EJ. The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics. *Neurosci Biobehav Rev.* 2003;27(7):593-604.
2. Cummings JL. Frontal-subcortical circuits and human behavior. *Arch Neurol.* 1993;50(8):873-880.

SLIDE 3

Cortical Thickness in ADHD

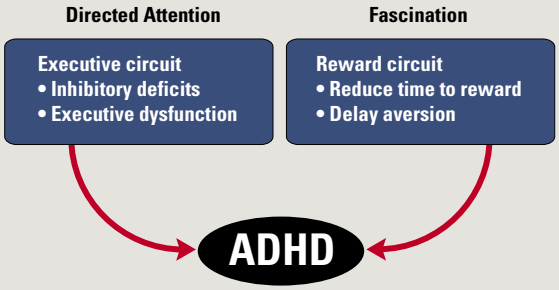


Cortical thinning of the cingulo-frontal-parietal attention network in adults with ADHD

Makris N, Biederman J, Valera EM, et al. Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. *Cereb Cortex.* 2007;17(6):1364-1375. Reprinted with permission from *Cerebral Cortex*, (Copyright 2007), Oxford University Press. All rights reserved.

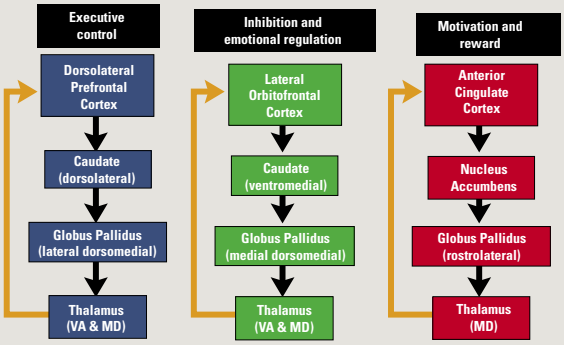
SLIDE 4

Toward a Dual Pathway Model[1]



SLIDE 5

Frontosubcortical Circuits[2]



TREATING ADULT ADHD WITH STIMULANTS

By Mark A. Stein, PhD

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SLIDE

Long-Acting ADHD Preparations

Methylphenidate Formulations

	Duration of Effect	***Dose***
Concerta®	10-12+ hours	once daily
Metadate® CD	8 hours	once daily
Ritalin® LA	8 hours	once daily
Focalin XR	10–12 hours	once daily
Daytrana	10–12+ hours	once daily

Amphetamine-Based Formulations

	Duration of effect	***Dose***
Adderall XR®	8–12 hours	once daily
Dexedrine®	4–6 hours	2–3 X daily
Adderall®	4–6 hours	2–3 X daily
Dexedrine® Spansule	6–8 hours	1–2X daily
Vyvanse	10–14 hours	1X daily

NONSTIMULANTS AND EMERGING TREATMENTS IN ADULTS WITH ADHD

By Jeffrey H. Newcorn, MD

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SLIDE 1

Nonstimulants Used in ADHD

Tricyclic antidepressants

- Numerous studies demonstrating efficacy
- Usage limited by several sudden cardiac deaths

α_2 Agonists (eg, clonidine, guanfacine)

- Extensive use but minimal controlled efficacy data
- Cardiac AEs; possibly worse with MPH co-administration
- Extended-release guanfacine is FDA approvable and may be available in 2009

Newer antidepressants

- Bupropion (several controlled studies; 1 multi-site)
- Venlafaxine (open studies only)

Atomoxetine

- Only FDA-approved agent; youth and adults
- No serious cardiac AEs in premarketing trials

AEs=adverse events; MPH=methylphenidate; FDA=Food and Drug Administration

SLIDE 2

Differential Respone to Atomoxetine (ATX) and Methylphenidate[1]

	Responders to ATX	***Non-responders to ATX***	***Total***
Responders to OROS®	76	24	100
Nonresponders to OROS®	29	35	64
Total	105	59	164

* ≥40% Reduction in ADHD-RS Total Score; *P*<.001, Fisher's exact test.

SLIDE 3

Environmental Modifications for Individuals with ADHD

Structure environment

- Identify and avoid distracting environments eg, shop in smaller stores, avoid working in cubicles
- Organize physical space (eg, label cupboards)
- Establish centers (eg, for bills, messages)

Alter communication regarding tasks and establish methods for implementation

- Examples: structure time, brief instructions, create work interests

Use external aids:

- Examples: electronic calendars with day planners, tape recorders, note pads, checklists, reminder alarms, and various task-specific devices (eg, pillboxes or key finders)

Reference

1. Newcorn JH, Kratochvil CJ, Allen AJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. *Am J Psychiatry.* 2008;165(6):721-730.

BEST PRACTICES IN ADULT ADHD: NEUROBIOLOGY, PHARMACOLOGY, AND EMERGING TREATMENTS

CME QUESTIONS

1. **A recent study by Mick and colleagues reported that the highest risk factor for attention-deficit/hyperactivity disorder (ADHD) was:**

   A. Low birth weight
   B. Psychosocial adversity
   C. Prenatal drug exposure
   D. Parental ADHD

2. **Measurements of cortical thickness in ADHD versus controls show?**

   A. A reverse pattern of development of cortical thickness (associative to somatosensory cortices)
   B. No differences
   C. The same pattern of development of cortical thickness (somatosensory to associative cortices) but delayed
   D. Slower development with medication exposure

3. **The percentage of the etiology of ADHD attributable to genes (heritability) is:**

   A. 10%
   B. 20%
   C. 50%
   D. 75%

4. **All of the following are Food and Drug Administration-approved treatments for adults with ADHD except:**

   A. Mixed amphetamine salts
   B. Atomoxetine
   C. Bupropion
   D. Dexmethylphenidate extended release

5. **The relationship between age and optimal dose is complex, requiring titration.**

   A. True
   B. False

6. **Which of the following is a rationale for nonstimulant treatment of ADHD?**

   A. Effective nonstimulants for ADHD modulate noradrenergic neurotransmission
   B. A percentage of individuals treated with stimulants do not achieve an optimal response, even if multiple medications are tried
   C. There are some individuals who will not agree to treatment with stimulants, even if they are counseled regarding the generally advantageous risk/benefit profile
   D. Poor tolerability to stimulants limits treatment in a subset of individuals
   E. All of the above

7. **More recent studies suggest similar effect sized in treating ADHD in children and adults:**

   A. True
   B. False

8. **Which of the following nonstimulant medications have been shown to be effective in controlled trials in adults with ADHD?**

   A. Atomoxetine
   B. Clonidine
   C. Venlafaxine
   D. A and B
   E. A, B, and C

REGISTRATION

OCTOBER 2008 CME POSTTEST

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ANSWER FORM

Expert Roundtable PsychCast™ – Best Practices in Adult ADHD: *Neurobiology, Pharmacology, and Emerging Treatments*

TERMINATION DATE: October 31, 2010

To receive credit, you should score 70% or better (participants will receive certification for their records in approximately 4–6 weeks). Early submission of this posttest is encouraged. Please submit this test by October 1, 2010, to be eligible for credit. If you have any questions about this, or any of our other CME materials, please e-mail CME@mblcommunications.com

Please circle your answers

1. A B C D 2. A B C D 3. A B C D 4. A B C D 5. A B 6. A B C D E 7. A B 8. A B C D E

EVALUATION SECTION (please provide the information below and print clearly)

1. Was this activity relevant to your practice? Yes ❑ No ❑
2. Were the following objectives met?
   - A. Review the neurobiology of attention-deficit/hyperactivity disorder (ADHD), including genetic influences and neuroanatomical and neurochemical factors. Yes ❑ No ❑
   - B. Describe the current practices and controversies surrounding stimulant therapy in adults with ADHD. Yes ❑ No ❑
   - C. Discuss the benefits of nonstimulant treatment, psychosocial treatment, and emerging treatment options for adult ADHD. Yes ❑ No ❑
3. Did this activity increase your knowledge and/or skills in delivering patient care? Yes ❑ No ❑
4. Does the information you received from this CME activity confirm the way you presently manage your patients? Yes ❑ No ❑
5. Will the information you received from this CME activity change the way you will manage your patients in the future? Yes ❑ No ❑

   If you answered yes, what change(s) do you intend to make in your practice? _____
6. Did this CME activity provide a balanced, scientifically rigorous presentation of therapeutic options related to the topic without commercial bias and influence? Yes ❑ No ❑
7. Do you feel these topics should be repeated/updated in future CME activities? Yes ❑ No ❑

   If you answered yes, what suggestions would you make to improve this activity? _____
8. Was the format of this activity appropriate for the content being presented? Yes ❑ No ❑
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   ❑ Print media ❑ Internet text ❑ Internet multi-media ❑ Live meeting ❑ PDA ❑ Podcast
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