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THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE

CME PSYCHCAST™

ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THE ROLE OF DEPRESSION

FACULTY

Timothy E. Wilens, MD, Andrew A. Nierenberg, MD,
Anthony L. Rostain, MD, and Thomas J. Spencer, MD

SECTION EDITOR

David L. Ginsberg, MD

CME 1

ABSTRACT

Adult attention-deficit/hyperactivity disorder (ADHD) and depressive disorders have high overlapping prevalence rates. It is becoming increasingly clear that depression in individuals with ADHD is not an artifact of ADHD, nor is ADHD in individuals with depression an artifact of depression. The comorbidity of these disorders raises significant issues for diagnosis and treatment. Patients with both disorders often underreport their symptoms or have difficulty presenting a comprehensive picture of their conditions. To make an accurate diagnosis, clinicians must conduct a cognitive assessment accounting for both the patient's presenting complaints and history. In addition, patients' negative core beliefs and views must be assessed at diagnosis and addressed in the comprehensive treatment approach. In the treatment algorithm for both disorders, physicians should prioritize the worse condition. However, because depression is often viewed as the worse condition, physicians may be reluctant to treat comorbid ADHD. Physicians must recognize that comorbid ADHD carries a host of additional academic, occupational, and cognitive symptoms that demand treatment simultaneous to or following treatment for depression. Combined pharmacotherapy for ADHD and comorbid depression is often necessary and should be seriously considered. Approved pharmacologic treatments include stimulants and nonstimulants, while experimental treatments include antidepressants and arousal agents.

In this Expert Roundtable PsychCast™, Andrew A. Nierenberg, MD, discusses the epidemiology of depression and the neurologic theories behind depression and its treatment; Anthony L. Rostain, MD, explains the prevalence and clinical presentation of adult ADHD and comorbid depression; Timothy E. Wilens, MD, provides an overview of pharmacotherapy for comorbid adult ADHD and depression; and Thomas J. Spencer, MD, discusses treatment options for patients with these comorbid conditions.



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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: April 23, 2008.

Faculty Affiliations

Timothy E. Wilens, MD, is associate professor of psychiatry in the Department of Psychiatry at Harvard Medical School and director of substance abuse services in the Clinical and Research Program in Pediatric Psychopharmacology at Massachusetts General Hospital in Boston.

Andrew A. Nierenberg, MD, is associate director of the Depression Clinical and Research Program at Massachusetts General Hospital and professor of psychiatry at Harvard Medical School in Boston.

Anthony L. Rostain, MD, is professor of psychiatry and pediatrics and director of the Adult ADHD Treatment and Research Program at the University of Pennsylvania School of Medicine in Philadelphia.

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.

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 Disclosure

Dr. Wilens is a consultant for Abbott, Cephalon, Eli Lilly, Ortho-McNeil, Merck, the National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), Novartis, and Shire; is on the speaker's bureaus of Ortho-McNeil, Novartis, and Shire; and receives grant support from Abbott, Eli Lilly, Ortho-McNeil, Merck, NIH, NIDA, and Shire. Dr. Wilens' presentation includes discussion of unapproved/investigational uses of treatments for adult attention-deficit/hyperactivity disorder.

Dr. Nierenberg is a consultant to or serves on the advisory boards of AstraZeneca, Brain Cells, Bristol-Myers Squibb, Eli Lilly, Jazz, Merck, the National Institute of Mental Health (NIMH), Novartis, and Schering-Plough; and receives research support from the NIMH and Pfizer.

Dr. Rostain has received honoraria from Eli Lilly and Ortho-McNeil; and serves on the advisory board of Shire.

Dr. Spencer is on the advisory boards of Cephalon, Eli Lilly, GlaxoSmithKline, McNeil, Novartis, Pfizer, and Shire; is on the speaker's bureaus of Eli Lilly, GlaxoSmithKline, Ortho-McNeil, Novartis, and Shire; and receives research support from Cephalon, Eli Lilly, GlaxoSmithKline, Ortho-McNeil, Novartis, and Shire. Dr. Spencer's presentation includes discussion of unapproved/investigational uses of atomoxetine, fluoxetine, paroxetine, and venlafaxine.

Peer Reviewers

David L. Ginsberg, MD, receives honoraria from AstraZeneca and GlaxoSmithKline.

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

Learning Objectives

- Evaluate recent research on the genetic and biologic evidence for associations between attention-deficit/hyperactivity disorder (ADHD) and depression.
- Assess the treatments that would benefit patients with ADHD and comorbid depression and the risks of treating this patient subgroup.

Statement of Need and Purpose

Although attention-deficit/hyperactivity disorder (ADHD) has traditionally been considered a pediatric disorder, up to 65% of children with a diagnosis of ADHD continue to display behavioral problems and symptoms of the disorder into their adult lives. Adults with ADHD demonstrate functional impairments in multiple domains, often including poor educational performance, occupational problems, and relationship difficulties. Accurate diagnosis of ADHD in adults is challenging and requires careful consideration of other psychiatric and medical disorders that may mimic symptoms of the disorder. The majority of adults with ADHD exhibit at least one comorbid psychiatric disorder, which may confound a proper ADHD diagnosis. Comorbidity between ADHD and major depressive disorder has been reported from both epidemiologic and clinical studies of both children and adults. Stimulants and noradrenergic and dopaminergic antidepressants have been shown to be useful medical interventions for adult ADHD. Cognitive-behavioral skills training and psychotherapy are useful adjuncts to pharmacotherapy. Devising a treatment plan for comorbid adult ADHD requires careful consideration, and treating the depression may improve ADHD symptoms such as inattention and irritability. Education is needed to increase the detection and treatment of adult ADHD and research is necessary to determine whether effective treatment would reduce the onset, persistence, and severity of disorders that co-occur with adult ADHD.

Target Audience

This activity is designed to meet the educational needs of psychiatrists.

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.



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Credit Designation

The Mount Sinai School of Medicine designates this educational activity for a maximum of 1 *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 June 1, 2010 to be eligible for credit.



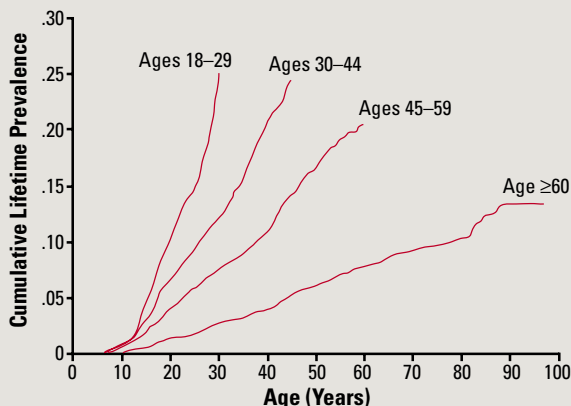
MAJOR DEPRESSIVE DISORDER: EPIDEMIOLOGY, COURSE OF ILLNESS, AND TREATMENT

By Andrew A. Nierenberg, MD

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SLIDE 1

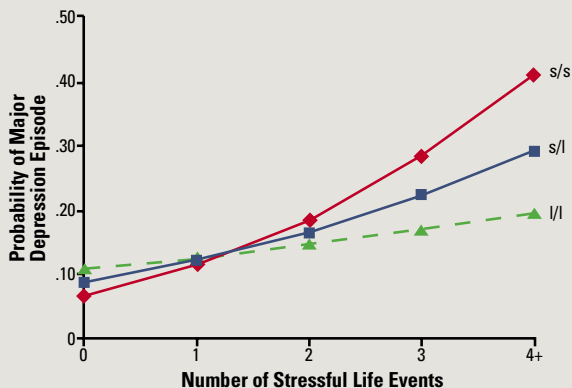
Major Depressive Disorder Cohort Effect



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SLIDE 3

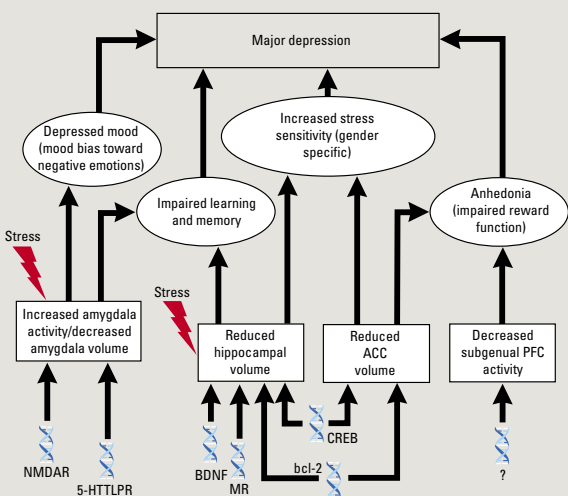
S allele Promoter Region 5-HTTLPR Interacts with Environment



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SLIDE 2

Neuroanatomical Abnormalities in Major Depression

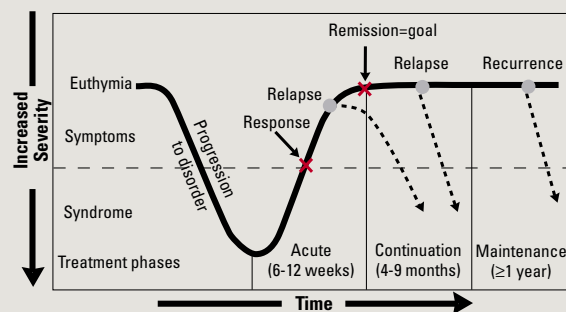


ACC=anterior cingulate cortex; PFC=prefrontal cortex; NMDAR=selective N-methyl-D-aspartate receptor; BDNF=brain-derived neurotrophic factor; MR=mineralocorticoid receptors; CREB=cAMP response element binding.

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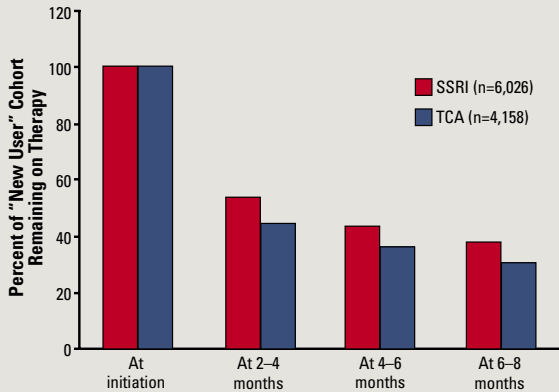
SLIDE 4

Treatment Outcomes in Major Depression¹



SLIDE 5

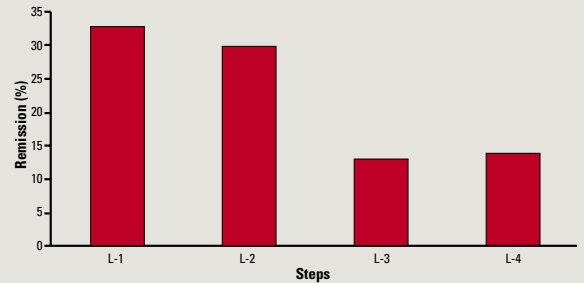
Few Continue Taking Medications



SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.
 Reprinted from *Aust N Z J Psychiatry*. 2004;38(6):450-454. Copyright 2004, Taylor & Francis Ltd. All rights reserved.

SLIDE 6

*STAR*D: Overall Remission Rate by Treatment Steps*



STAR*D=Sequenced Treatment Alternatives to Relieve Depression.

Reference

1. Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry*. 1991;52(suppl 5):28-34.



**ADULT ADHD AND DEPRESSIVE DISORDERS:
 PREVALENCE, SIGNIFICANCE, AND CLINICAL
 PRESENTATION**

By Anthony L. Rostain, MD

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SLIDE 1

Rates of MDD in Adults Diagnosed with Adult ADHD¹

	ADHD (N=146)	Clinical (N=97)	Community (N=109)
Current MDD	13%	14%	1%
Past MDD	23%	19%	7%
Ever MDD	36%	33%	8%

SLIDE 2

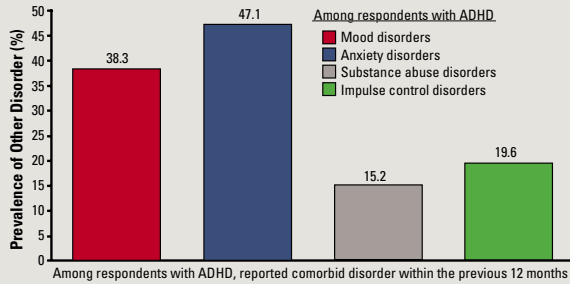
Rates of Dysthymia in Adults Diagnosed with ADHD¹

	ADHD (N=146)	Clinical (N=97)	Community (N=109)
Current Dysthymia	25%	13%	0%
Past Dysthymia	1%	3%	0%
Ever Dysthymia	27%	16%	0%

SLIDE 3

Comorbidity of Other DSM-IV-TR Disorders with ADHD in Adults²

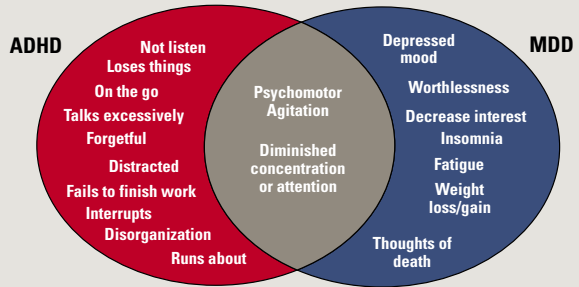
National Comorbidity Survey Replication (N=3,199)



DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.

SLIDE 6

Overlap of DSM-IV Criteria for ADHD and MDD

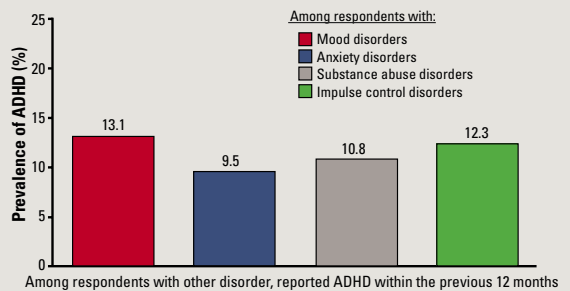


DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MDD=major depressive disorder.

SLIDE 4

Comorbidity of ADHD with Other DSM-IV-TR Disorders in Adults²

National Comorbidity Survey Replication (N=3,199)



DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.

SLIDE 7

ADHD and MDD Differential Diagnosis

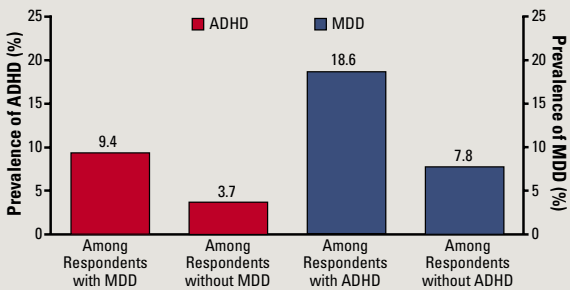
Symptom	ADHD	MDD
Hyperactivity	++	±
Inattention	++	++
Talkativeness	++	—
School dysfunction	++	+
Effect of structure	++	±
Oppositional defiant or conduct disorder	++	++
Onset	<7 years	Variable
Course	Constant	Chronic/cycle
Irritability	+	+++
Depression	±	+++
Substance abuse	+	+
Global dysfunction	+	++
Family History	ADHD Proband	MDD Proband
ADHD	+++	++
Depression	++	+++

MDD=major depressive disorder; —=no association of symptom with diagnosis; ±=possible association; +=mild association; ++=moderate association; +++=strong association.

SLIDE 5

Comorbidity of Adult ADHD with MDD in Adults²

National Comorbidity Survey Replication (N=3,199)



References

1. Barkley R, Murphy KR, Fischer M. *ADHD in Adults: What the Science Says*. New York: Guilford Press; 2008.
2. 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(4):716-723.



PHARMACOTHERAPY OF ADHD IN ADULTS

By Timothy E. Wilens, MD — Moderator

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SLIDE 1

Adult ADHD Pharmacotherapeutic Options¹

Stimulants

- Dexmethylphenidate (Focalin XR*)
- Methylphenidate (Ritalin, Concerta, MTS, others)
- Amphetamine compounds (Adderall, Adderall XR*, LDX*)

Nonstimulant

- Atomoxetine (Strattera)*

Antidepressants (second-line)

- Bupropion (Wellbutrin)
- Tricyclic antidepressants

Arousal agent

- Modafinil (Provigil)

Research

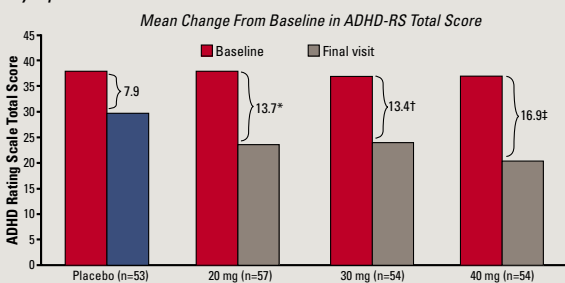
- Nicotinic/cholinergic modulators
- Alternative stimulant preparations

* FDA approved.

LDX=lisdexamfetamine.

SLIDE 2

D-Methylphenidate XR Significantly Reduced ADHD Total Symptom Scores²



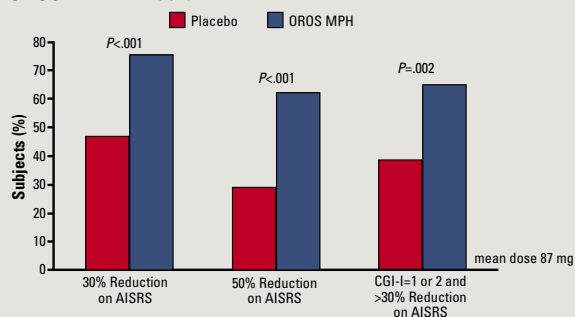
5-week study. D-Methylphenidate XR 20 mg is currently the maximum dose approved in adults.

* $P < .01$; † $P < .05$; ‡ $P = .001$ vs placebo.

ADHD-RS=Attention-Deficit/Hyperactivity Disorder Rating Scale; XR=extended release.

SLIDE 3

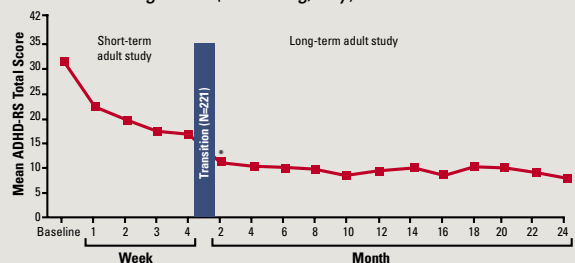
OROS MPH in Adult ADHD³



OROS MPH=osmotic-release methylphenidate; AISRS=Adult ADHD Investigator Symptom Report Scale; CGI-I=Clinical Global Impressions-Improvement.

SLIDE 4

Symptom Improvement with Mixed Amphetamine Salts XR Short- and Long-Term (20–60 mg/day)⁴

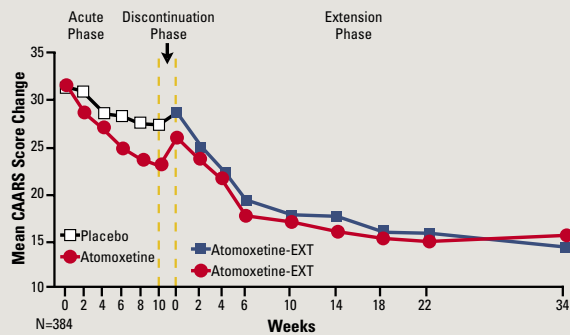


* $P < .05$ by 1-sample t -test of mean change from baseline of long-term study; last observation carried forward.

ADHD-RS=Attention-Deficit/Hyperactivity Disorder Rating Scale.

SLIDE 5

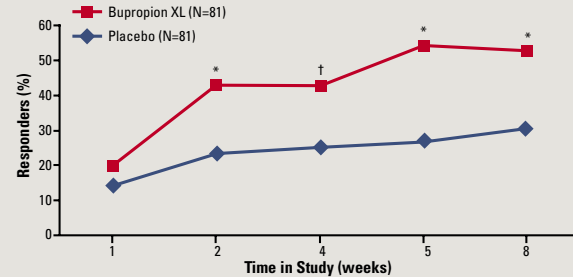
Atomoxetine: Long-Term Efficacy in Adults⁵



CAARS=Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scales.

SLIDE 6

Bupropion XL in Adults With ADHD⁶



*P<.01; †P<.05.

References

1. Wilens TE. Drug therapy for adults with attention-deficit hyperactivity disorder. *Drugs*. 2003;63(22):2395-2411.
2. Spencer TJ, Adler LA, McGough JJ, et al. Efficacy and safety of dexamethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2007;61(12):1380-1387.
3. 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(9):829-835.
4. Biederman J, Mick E, Spencer T, et al. An open-label trial of OROS methylphenidate in adults with late-onset ADHD. *CNS Spectr*. 2006;11(5):390-396.
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6. Wilens TE, Haight BR, Horrigan JP, et al. Bupropion XL in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled study. *Biol Psychiatry*. 2005;57(7):793-801.



TREATMENT OF ADULT ADHD AND COMORBID DEPRESSION

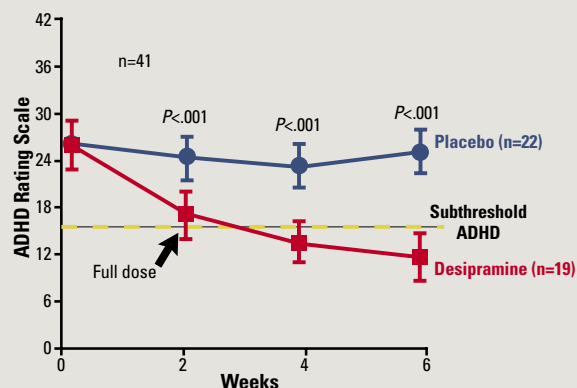
By Thomas J. Spencer, MD

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SLIDE 1

Desipramine* Efficacy in Adults¹

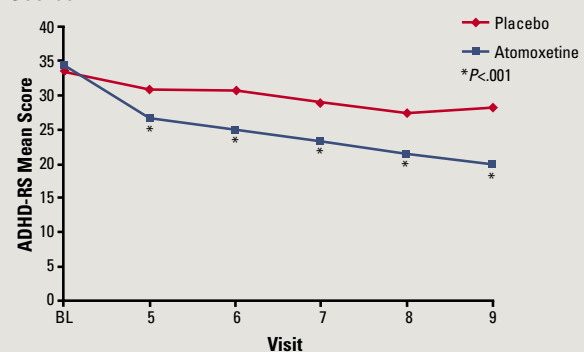
Randomized, double-blind, placebo-controlled study[†]



* Not FDA-approved for ADHD. † Titration to 200 mg over 2 weeks.

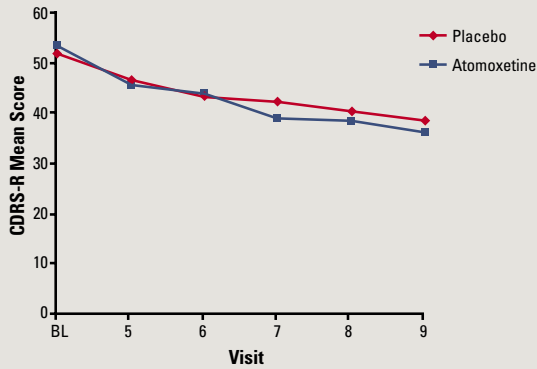
SLIDE 2

Attention-Deficit/Hyperactivity Disorder Rating Scale Total Scores²



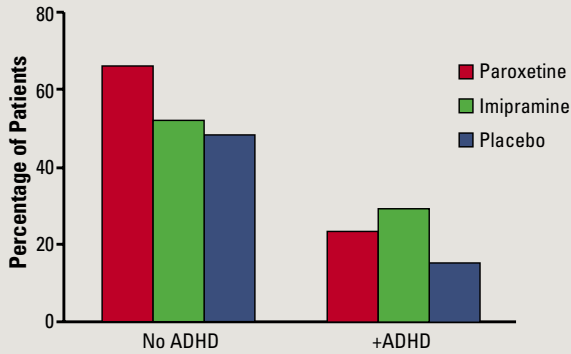
SLIDE 3

Children's Depression Rating Scale, Revised, Total Scores²



SLIDE 4

Response to Antidepressant Treatment in Depressed Youth ± Comorbid ADHD (n=271)³



SLIDE 5

Combined Pharmacotherapy

Anti-Depression Treatment Anti-ADHD Treatment

- | | |
|--|---|
| <ul style="list-style-type: none"> • Antidepressants Bupropion SSRIs Combined noradrenergic/serotonergic Tricyclics MAOIs | <ul style="list-style-type: none"> • Stimulants • Catecholaminergic Antidepressants • Alpha agonists |
|--|---|

SSRIs=selective serotonin reuptake inhibitors; MAOIs=monoamine oxidase inhibitors.

References

1. DuPaul G, Barkley R, McMurray M. Response of children with ADHD to methylphenidate: Interaction with internalizing symptoms. *J Am Acad Child Adolesc Psychiatry.* 1994;33:894-903.
2. Bangs ME, Emslie GJ, Spencer TJ, et al. Efficacy and safety of atomoxetine in adolescents with attention-deficit/hyperactivity disorder and major depression. *J Child Adolesc Psychopharmacol.* 2007;17(4):407-420.
3. Birmaher B, McCafferty JP, Bellew KM, et al. Comorbid ADHD and disruptive behavior disorders as predictors of response in adolescents treated for major depression. Poster presented at: Annual Meeting of the American Psychiatric Association; May 13-18, 2000; Chicago, IL. Abstract NR562:209.

ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THE ROLE OF DEPRESSION

CME QUESTIONS

1. Which of the following statements is true?

- A. Remission rate in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) was ~50%
- B. Remission rate in STAR*D was ~30%
- C. Of those who remitted in STAR*D, 30% did so within 6 weeks
- D. Of those who remitted in STAR*D, 30% did so within 8 weeks

2. Overall rates of mood disorders in patients with attention-deficit/hyperactivity disorder (ADHD) is most likely to be:

- A. 10%
- B. 20%
- C. 30%
- D. 40%
- E. 50%

3. Family histories of depression are seen in probands with ADHD, and vice versa at similar rates.

- A. True
- B. False

4. The following medications have not been shown to be effective in adults with ADHD:

- A. Atomoxetine
- B. d-methylphenidate
- C. Mixed amphetamine salts extended release
- D. Divalproex

5. The following medications have efficacy in ADHD:

- A. Mood stabilizers
- B. Stimulants
- C. Selective serotonin reuptake inhibitors
- D. Diazepam

6. Most studies show stimulants treat ADHD in the context of depression and/or anxiety (versus ADHD without depression and/or anxiety):

- A. More effectively
- B. Equally effectively
- C. Less effectively

7. The recent controlled study of atomoxetine for children with both depression and ADHD found that atomoxetine was effective for:

- A. Both ADHD and depression
- B. Neither ADHD and depression
- C. Depression but not ADHD
- D. ADHD but not depression

8. The recent study of bupropion for children with both depression and ADHD found that bupropion was effective for:

- A. ADHD independently of depression response
- B. Neither ADHD nor depression
- C. ADHD only if depression improved

REGISTRATION

JUNE 2008 CME POSTTEST

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ANSWER FORM

Expert Roundtable PsychCast™ – Adult Attention-Deficit/Hyperactivity Disorder and the Role of Depression

TERMINATION DATE: June 30, 2010

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Please circle your answers

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

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. Evaluate recent research on the genetic and biologic evidence for associations between ADHD and depression Yes No B. Assess the treatments that would benefit patients with ADHD and comorbid depression and the risks of treating this patient subgroup 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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