ADHD and Comorbid Disorders in Adults

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the planning teleconference series "ADHD and Comorbid Disorders in Adults," which was held in January and February 2008. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Eli Lilly and Company.*

The planning teleconference was chaired by ***Lenard A. Adler****, M.D., Departments of Psychiatry, Neurology, and Child and Adolescent Psychiatry, New York University School of Medicine, New York. The faculty were* ***Russell A. Barkley****, Ph.D., Department of Psychiatry, State University of New York Upstate Medical University, Syracuse; and* ***Jeffrey H. Newcorn****, M.D., Department of Psychiatry, Mount Sinai School of Medicine, New York, N.Y.*

Financial disclosure: ***Dr. Adler*** *has received grant/research support from Abbott, Cortex, Bristol-Myers Squibb, Merck, Novartis, Pfizer, Shire, Eli Lilly, Ortho-McNeil/Janssen/Johnson & Johnson, New River Pharmaceuticals, Cephalon, and the National Institute on Drug Abuse; is a member of the speakers bureaus for Eli Lilly and Shire; and is a member of the advisory boards and is a consultant for Abbott, Cortex, Novartis, Pfizer, Shire, Eli Lilly, Ortho-McNeil/Janssen/Johnson & Johnson, New River Pharmaceuticals, Cephalon, Merck, Organon, Sanofi-Aventis, and Psychogenics.* ***Dr. Barkley*** *is a consultant for Eli Lilly, Shire, and Abbott; has received grant/research from the National Institute of Mental Health; has received honoraria from the Canadian Attention Deficit Hyperactivity Disorder Resource Alliance, the Campus Alcohol and Drug Education Center of California State University, the Learning Disabilities-Attention Deficit Disorder Program of North Carolina, ThedaCare, the National Association of School Psychologists, the Medical College of Wisconsin, the New England Educational Institute, Egleston Children's Hospital, Spanish Child Psychiatry Association, the Portugal ADHD Foundation, the Brazil ADHD Parents Association, the Uruguay ADHD Parents Association, and the Argentina Mental Health Conference; is a member of the speakers/advisory boards for Eli Lilly, Shire, Novartis, and Janssen; and has received other financial or material support from Guilford Publications, Compact Clinics, the New England Educational Institute, and J & K Seminars.* ***Dr. Newcorn*** *is an advisor/consultant for Eli Lilly, McNeil, Shire, Lupin, Sanofi-Aventis, Abbott, and Psychogenics; has received grant/research support from Eli Lilly and McNeil; and has received honoraria for speaking from Eli Lilly, Shire, and Novartis.*

The opinions expressed herein are those of the faculty and do not necessarily reflect the views of the CME provider and publisher or the commercial supporter.

Diagnostic Challenges in Identifying ADHD in Adults

In the United States, approximately 4.4% of adults have attention-deficit/hyperactivity disorder (ADHD),[1] and the average worldwide prevalence in adults is about 3.4%.[2] However, in the United States, only about 1 in 10 adults with ADHD is currently treated specifically for ADHD.[2] Adults with ADHD are likely to have adaptive impairments, evidenced by educational difficulties, a history of erratic employment, relationship and marital difficulties, credit or money problems, driving problems, risky sexual behavior, early parenthood, legal difficulties, poor physical health, and substance abuse problems.[2–5] Additionally, adults with ADHD commonly have comorbid disorders, such as mood and anxiety disorders or sleep problems, which may mask the symptoms of ADHD. Russell A. Barkley, Ph.D., discussed criteria for diagnosing ADHD in adults.

Current Consensus Definition of ADHD

In the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR),[6] ADHD is conceptualized as a developmental disorder of age-inappropriate inattention and hyperactivity that arises before 7 years of age. The disorder is recognized by severe behavioral and cognitive symptoms that cause impairment in 2 or more settings.

The disorder may occasionally develop in adolescence or adulthood, secondary to an acquired injury to the brain. Head trauma, stroke, tumor, or other insults to the brain, particularly injury to the frontal lobes and the connections to the striatum or basal ganglia, can mimic ADHD symptoms and warrant the diagnosis of acquired ADHD.

Diagnosis of adult ADHD cannot be based solely on a high level of symptoms or the patient's belief that he or she has the disorder; evidence must show that the patient's life is impaired by consequences of the symptoms. Comorbid disorders, such as depression, anxiety, conduct disorder, and antisocial personality disorder may occur with ADHD, but a diagnosis of ADHD can be made only when those other disorders do not fully account for the symptoms.

Problems With the Current Diagnostic Criteria for ADHD in Adults

The DSM-IV-TR criteria for ADHD were developed for diagnosing children and were not intended for use in adults. Because of differences between adult and childhood ADHD, Dr. Barkley suggested modifications in the criteria for diagnosis of ADHD in adults.

Symptom descriptions. Given that the majority of children with ADHD continue to have the disorder in adulthood,[7] the DSM-IV-TR descriptions of ADHD symptoms need to be adjusted for adults.[8] For example, the hyperactive and impulsive symptoms prominent in childhood become internalized with age[7]; as adults, these individuals feel a mental restlessness and a need to be busy, although they may complete few activities. Whereas children may exhibit behavioral impulsiveness, adults are likely to show impulsive decision making and verbal impulsiveness, which produces symptoms such as excessive talking, blurting out answers, and not letting others finish speaking.[9] Dr. Barkley added that the inattention attributed to ADHD probably represents impairment in executive functioning or the cognitive abilities that are used to regulate behavior.[10]

The executive deficits related to inattentive symptoms become increasingly prominent and impairing by adulthood. Descriptions of symptoms in adults need to include problems with time management, working memory, risk-taking, and impulse control.

Developmentally referenced cutoffs. Cutoff scores need to be adjusted for adults, according to Dr. Barkley. The DSM-IV-TR threshold of 6 of 9 symptoms required for diagnosis of ADHD is too high for adults.[11] Dr. Barkley recommended that clinicians use a threshold for adults of 4 of 9 symptoms, which can still constitute meaningful dysfunction.

Sex-referenced rating scales. The DSM-IV-TR criteria for ADHD were developed in a field trial comprising more boys than girls,[8] thus weighting the criteria toward male symptomatology. Dr. Barkley suggested that clinicians employ sex-referenced rating scales, such as the Conners' Adult ADHD Rating Scales[12] (CAARS), that have separate norms for women and men to better assess ADHD symptoms in women.

Age at onset. The DSM-IV-TR diagnostic criteria for ADHD require onset of symptoms prior to 7 years of age.[8] Dr. Barkley stated that when the criteria are revised, an age at onset prior to 16 years of age will likely be specified for adult ADHD. No precise age will be required because patient and family reports of the age at onset are often unreliable in adults.[5]

Developmental deviance. The DSM-IV-TR criteria do not specify how to establish developmental inappropriateness for the symptoms of inattention and hyperactivity or impulsivity. Dr. Barkley suggested that clinicians use the 93rd percentile, or 1.5 standard deviations above the mean, on a well-normed rating scale of ADHD symptoms for adults as the indicator of developmental deviance.[5,8]

Corroboration of reports. For a diagnosis of ADHD in adults, a requirement should be added that clinicians obtain and document corroborative information about symptoms and impairments described by the patient. Patients under age 30 years tend to underreport the severity of symptoms and impairments in current major life activities.[5] Conversely, overreporting of symptoms or malingering can also occur, especially in instances where some financial or legal outcome is contingent on the evaluation.

To corroborate the patient's history, clinicians should identify family members, close friends, or a spouse or partner with long-term knowledge of the patient. Parents may occasionally minimize their description of childhood symptoms because of remorse for failing to seek treatment earlier. If no one is available for corroboration, clinicians can review any available school, driving, or criminal records that might indicate problems in adolescence or earlier. When no corroboration is available, clinicians should listen carefully to the patient's history for pervasive impairments in numerous domains.

Definition of impairment. Dr. Barkley stressed that impairment is a requirement for the diagnosis of ADHD. The DSM-IV-TR does not define the term *impairment*, but according to the Americans With Disabilities Act of 1990,[13] impairment substantially limits 1 or more major life activities. Patients should be compared with the average person in the population rather than a high-functioning peer group; the term *impairment* cannot be applied because an individual's behavior and its consequences fall below expectations for the patient's level of intelligence.[11]

Major life activities. The major adult life activities of marriage, child-rearing, managing money, driving, sexual activity, and social relationships need to be added to the diagnostic criteria for home, school, and work settings currently specified in DSM-IV-TR. Adults with ADHD have problems handling these daily responsibilities.

Table 1. Proposed Criteria for ADHD in Adults[a]

1. Often is easily distracted by extraneous stimuli (DSM-IV-TR)
2. Often makes decisions impulsively (EF)
3. Often has difficulty stopping activities or behavior when he or she should do so (EF)
4. Often starts a project or task without reading or listening to directions carefully (EF)
5. Often shows poor follow-through on promises or commitments made to others (EF)
6. Often has trouble doing things in their proper order or sequence (EF)
7. Often drives a motor vehicle much faster than others (excessive speeding) (EF). For nondrivers, often has difficulty engaging quietly in leisure or enjoyable activities
8. Often has difficulty sustaining attention in tasks or recreational activities (DSM-IV-TR, optional)
9. Often has difficulty organizing tasks and activities (DSM-IV-TR, optional)
Cutoff: Either 4 of the first 7 or 6 of 9 symptoms
Age at onset: Childhood to adolescence (< 16 years of age)

[a]Adapted with permission from Barkley.[5]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition-Text Revision, EF = executive function.

Identifying Symptoms of ADHD in Adults

To identify symptoms appropriate for ADHD criteria in adults, a study[5] compared the following 3 groups: adults referred to a clinic for ADHD who were subsequently diagnosed with ADHD, a control group of adults referred to the same clinic who thought they had ADHD but did not (85% of whom were diagnosed with disorders other than ADHD), and a community control group. ADHD was diagnosed by a structured clinical interview using the DSM-IV-TR criteria but excluding age at onset.

The study[5] identified 9 essential symptoms for adults with ADHD, retaining only a few useful symptoms from DSM-IV-TR (Table 1). These requirements form a better set of criteria for adult ADHD than current criteria, according to Dr. Barkley.

Distractibility, making impulsive decisions, and executive deficits that

Table 2. Assessment Recommendations for Adult ADHD[a]

1. Obtain the patient's self-report of ADHD symptoms first for current functioning (using 4, not 6, of the DSM-IV-TR symptom criteria) and then for functioning before 16 years of age using DSM-IV-TR criteria
2. Obtain corroboration for symptoms and evidence of impairment in several major life activities in home, educational, and occupational domains as well as other domains of adult daily life
3. Obtain evidence of a chronic course without periods of remission, remembering that patients who put themselves in less demanding situations may reveal less impairment
4. Define impairment relative to the average person and not a high-functioning peer group
5. Explain impairment that developed later than age 16 years, such as special accommodations in schooling or self-medication
6. Use rating scales for adult ADHD
7. Rule out low IQ, specific learning disabilities, and other disorders such as anxiety or depression

[a]Based on Barkley et al.[5] and Barkley.[8]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition-Text Revision.

affect perseverance in activities or doing things in the correct sequence are better symptoms for identifying ADHD in adults than hyperactivity. However, attention problems cut across many psychiatric disorders and may not be particularly useful for differential diagnosis. A symptom that proved to be specific to adults with ADHD was problems with driving. Adults with ADHD have been found to be especially at risk for speeding citations and automobile accidents.[14]

Subtypes of ADHD. The subtypes of ADHD (i.e., inattentive, hyperactive/impulsive, and combined) specified in the DSM-IV-TR need to be revised, said Dr. Barkley. The hyperactive form of ADHD is rare in adults; children with this type of ADHD usually move into the combined type as executive and attention deficits develop.[11] Inattentive type ADHD needs to be reclassified into the following 3 groups: (1) people who have outgrown hyperactive symptoms and no longer meet all the criteria for combined type ADHD, (2) individuals who are 1 or 2 symptoms short of the 12 symptoms currently required for the combined type, and (3) a group that exhibits sluggish cognitive tempo, which comprises individuals who do not have difficulties with hyperactivity or impulse control but who appear shy or withdrawn; have problems with staring, daydreaming, passivity, or confusion; and have difficulties focusing on the important versus the unimportant.[15]

Conclusion

Dr. Barkley offered clinical guidelines for assessing adult ADHD (Table 2)[5,8] and stated that adult ADHD is a valid disorder that can be diagnosed using the DSM-IV-TR criteria with some adjustments. Although impairment in major life activities begins early in life for patients with ADHD, numerous issues that are less likely to be present in the diagnosis of children apply to the assessment and diagnosis of adults.

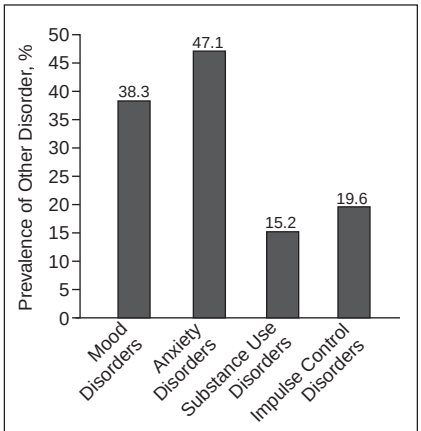
Managing ADHD and Comorbid Disorders

Jeffrey H. Newcorn, M.D., stated that the relationships and boundaries between ADHD and comorbid disorders are not well defined. Accurate diagnosis is difficult because comorbidities such as anxiety and learning difficulties may be concealed by more obvious ADHD symptoms, and conversely, ADHD symptoms may be concealed by more robust symptoms of severe depressive, conduct, bipolar, or substance use disorders (SUD). However, distinguishing among these disorders is important because they inform appropriate treatment.

Prevalence of Adult ADHD and Psychiatric Comorbidities

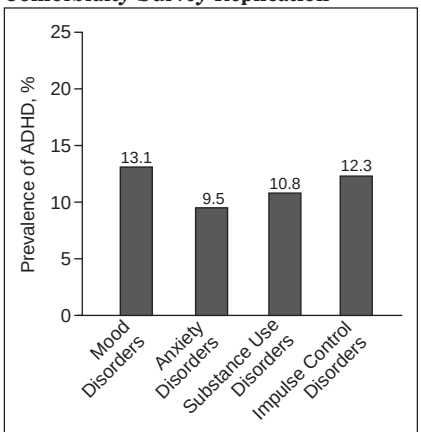
Comorbidity is common in adults with ADHD. Data from the National Comorbidity Survey Replication[1] showed that among 3199 respondents, adults with ADHD had substantial comorbidity with mood and anxiety disorders, SUD, and impulse control disorders within the previous 12 months (Figure 1), and adults with those disorders had substantial comorbidity with ADHD (Figure 2). However, Dr. Newcorn explained that comorbid

Figure 1. Prevalence of Other DSM-IV Disorders Among Respondents With Adult ADHD in the National Comorbidity Survey Replication[a,b]



[a]Data from Kessler et al.[1]
[b]$p < .05$ vs. respondents without another DSM-IV disorder.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 2. Prevalence of Adult ADHD Among Respondents With Other DSM-IV Disorders in the National Comorbidity Survey Replication[a,b]



[a]Data from Kessler et al.[1]
[b]$p < .05$ vs. respondents without ADHD.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 3. Rates of Psychiatric Disorders in Groups of Subjects With ADHD and in Adult Comparison Subjects Without ADHD[a]

	Referred Adults With ADHD (N = 84)		Nonreferred Adult Relatives With ADHD (N = 36)		Referred Children With ADHD (N = 140)		Comparison Adults Without ADHD (N = 207)	
Disorder	N	%	N	%	N	%	N	%
Oppositional disorder	24	29[b,c]	19	53[b]	92	66	5	2
Conduct disorder	17	20[b]	12	33[b,d]	30	21	8	4
Antisocial personality disorder	10	12[e]	6	18[b,f]	…	…	6	3
Major depressive disorder	26	31[b]	6	17[e]	40	29	11	5
Alcohol abuse	21	25[b,c]	6	17[c]	1	0.7	17	8
Alcohol dependence	23	27[c,e]	13	36[b,c]	2	1	27	13
Drug abuse	17	20[b,c]	7	19[c,e]	0	0	12	6
Drug dependence	15	18[b,c]	6	17[c]	1	0.7	12	6
Multiple anxiety disorders	42	50[b,d]	15	42[b]	39	28	28	14
Overanxious disorder	43	52[b,d,f]	14	40[b,f]	42	30	22	11
Separation anxiety disorder	6	7[d]	4	11	40	29	7	3
Generalized anxiety disorder	36	43[b]	7	20[b,f]	…	…	10	5
Agoraphobia	6	7[b]	1	3	13	9	1	0.5
Social phobia	27	32[b,d]	12	33[e]	18	13	27	13

[a]Adapted with permission from Biederman et al.[18]
[b]$p \le .001$ for comparisons with adults without ADHD by chi-square test (df = 1).
[c]$p \le .001$ for comparisons with children with ADHD by chi-square test (df = 1).
[d]$p \le .01$ for comparisons with children with ADHD by chi-square test (df = 1).
[e]$p \le .01$ for comparisons with adults without ADHD by chi-square test (df = 1).
[f]For this disorder, N did not match the total N because of missing values.
Symbol: … = Data not given.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

disorders may be a direct reflection of ADHD symptoms and their impact; for example, the experiences of doing poorly in certain academic activities such as tests in school may lead to anxiety regarding performance and low self-esteem regarding poor achievement. Some comorbid disorders, such as bipolar disorder, may actually be genetic variants of ADHD,[16] whereas other frequently occurring comorbid conditions, such as depressive disorders, share common environmental risk factors with ADHD.[17]

Differences in Comorbidity Across Age Groups

Comorbid disorders may differ between children and adults with ADHD. For example, a comparison[18] of children and adults with ADHD and comorbid psychiatric disorders found that children more often have comorbid oppositional defiant disorder, but adults with ADHD more often have comorbid anxiety disorders (Table 3), although interpretation is somewhat constrained by the size of some of the comorbid groups. Other comorbid disorders that often occur in adults are major depressive disorder (MDD) and SUD.[1] Some of the cognitive problems in ADHD are difficult to distinguish from learning disabilities, which may confuse differential diagnosis in adult patients who have a history of underachievement.[19] Additionally, personality disorders are common among adults who had ADHD in childhood.[20–22]

Adult ADHD and Specific Common Psychiatric Comorbidities

Mood and anxiety disorders. Dr. Newcorn advised that focusing on the developmental course of the patient's conditions can help distinguish whether mood and anxiety disorders are independent of or secondary to ADHD, which can have important implications for the sequencing of treatment. For example, if ADHD preceded an anxiety disorder, and the anxiety is specific to performance situations, the clinician might decide to treat the ADHD first and see whether improvement in ADHD symptoms produces a corresponding change in anxiety symptoms. However, if the conditions are relatively independent and the anxiety is greatly impairing, the anxiety should be treated at the same time or even first.

Substance abuse. Adults with ADHD have elevated rates of SUD and an earlier age at onset of SUD (19.1 vs. 22.0 years of age) compared with adults without ADHD.[23] Research has examined whether ADHD stimulant pharmacotherapy sensitizes individuals to increase the risk of using other stimulants, such as cocaine, later in life. Studies in humans suggest that this is not the case and have found either no effect of treatment on substance abuse[24,25] or a decrease in risk[26] that may result from treatment of impulsivity. The risk for substance abuse is particularly high among adolescents and young adults with ADHD, but Dr. Newcorn noted that the relationship between ADHD and early onset of substance abuse suggests that there may be a window of opportunity for treatment.

The only substance of abuse found to have a specific association with ADHD is nicotine.[27] Nicotine impacts neural circuits in the brain that enhance attention,[28] which may account for the specificity of risk in ADHD. Dr. Newcorn observed that nicotine may serve as a "gateway" drug for SUD, preceding the use of other substances of abuse and producing changes in neural function that increase addiction susceptibility. Nicotine use also has important psychosocial consequences. Smoking cigarettes is illegal for adolescents, and adolescents who smoke cigarettes are more likely to be exposed to peers who use other drugs or are involved in other illicit behaviors. Thus, targeting the potential for nicotine use and abuse among adolescents with ADHD is of paramount importance.

Learning disabilities. The impairments associated with ADHD can be increased by the co-occurrence of specific learning disabilities. A substantial number of children with ADHD have comorbid learning disabilities and continue to show cognitive and academic impairments in adolescence and

adulthood.[29] The consequences of learning disabilities among individuals with ADHD include academic underachievement, grade repetition, school dropout, and working below ability, all of which can influence adult job attainment and performance and therefore socioeconomic status.

Personality disorders. Individuals with disruptive behavior disorders are at increased risk for cluster B personality disorders (i.e., antisocial, borderline, histrionic, or narcissistic personality disorder),[20] and children with ADHD are at increased risk for antisocial personality disorder[21] and borderline personality disorder in adulthood.[22] Dr. Newcorn described a longitudinal study[30] in which the development of personality disorders in children with ADHD was tracked through adolescence and young adulthood. Increased rates of neuroticism and lower levels of conscientiousness and agreeableness were found in those with ADHD compared with matched controls. This was particularly the case among those whose ADHD was persistent, raising the question whether successful treatment of ADHD might decrease the risk of developing personality disorders.

Conclusion

Dr. Newcorn advised that clinicians assess patients with ADHD for comorbid disorders and assess patients with other psychiatric disorders for ADHD. Adults who have undiagnosed ADHD may visit a physician because of problems associated with a comorbid disorder, while children are more often brought in specifically for problems that relate to ADHD. He observed that it is important to identify comorbidity when it is present because comorbid disorders can affect the presentation and course of ADHD. In addition, comorbid disorders often require treatment independent of the treatment for ADHD. Distinguishing comorbidity from impairment secondary to ADHD can be difficult but is possible if clinicians understand the developmental course of the different conditions and take a detailed history.

Dr. Newcorn remarked that, because treatment of ADHD may have an impact on both the frequency and clinical manifestation of other disorders, the early identification and treatment of ADHD hopefully can alter the developmental course of both ADHD and these other disorders. While empirical data do not yet support this contention, prevention of comorbidity remains an appropriate goal of ADHD treatment as well as a potentially important direction for future research.

Safety and Efficacy of Stimulant and Nonstimulant Treatments for ADHD and Comorbid Disorders

Lenard A. Adler, M.D., first explained that 2 main classes of medication are used in the treatment of ADHD: stimulants and nonstimulants. Stimulants are either methylphenidate or amphetamine compounds; nonstimulant therapy is atomoxetine, a norepinephrine reuptake inhibitor. Two stimulants, mixed amphetamine salts extended-release (XR) and dexmethylphenidate XR, have U.S. Food and Drug Administration (FDA) approval for the treatment of ADHD in adults; the prodrug stimulant lisdexamfetamine has also received FDA approval. Atomoxetine is the only nonstimulant approved by the FDA for the treatment of adults with ADHD.

Pharmacotherapy for ADHD Alone

Stimulants. Studies of stimulants in adult ADHD have examined the efficacy of methylphenidate and amphetamine salts in immediate-release and extended-release formulations in adults with ADHD. The immediate-release forms have a duration of effect of 4 to 6 hours, whereas the extended-release forms have a duration of effect between 10 and 14 hours.

Dr. Adler cited a randomized study[31] of adults with ADHD (N = 146) who were treated for 6 weeks with either immediate-release methylphenidate or placebo. Reductions in ADHD symptoms with the active drug started at week 1, were statistically significant ($p < .001$) versus placebo response at week 2, and continued through week 6. The response rate for methylphenidate was 76% versus 19% for placebo.

Immediate-release mixed amphetamine salts were also found to be effective in adults with ADHD. In a study[32] that examined immediate-release mixed amphetamine salts versus placebo in a cohort of 27 adults with ADHD for 3 weeks, significant effects were found by week 2 and continued through week 3 ($p < .001$). The response rate for the active drug was 70% versus 7% for placebo.

Dr. Adler next presented data on sustained-release medications. Treatment with mixed amphetamine salts XR in 255 adults with ADHD was examined in a dose-ranging, multicenter, double-blind registration study.[33] After 4 and 12 hours, mixed amphetamine salts XR showed a statistically significant reduction in scores on the CAARS Short Version Self-Report ($p < .05$). Over the 4-week course of treatment, statistically significant improvement versus placebo was found on the ADHD-Rating Scale (ADHD-RS) ($p \leq .001$). However, a stepwise incremental improvement did not occur, and Dr. Adler noted that the package insert[34] states that doses above 20 mg/day have not shown adequate evidence of providing additional benefit.

Another extended-release stimulant that has been studied in adults with ADHD is dexmethylphenidate. Spencer and colleagues[35] examined several doses of dexmethylphenidate XR (20, 30, and 40 mg/day) versus placebo for 5 weeks and found a statistically significant mean change from baseline to endpoint on DSM-IV ADHD-RS total scores for all the doses studied ($p = .006$, $p = .012$, and $p < .001$, respectively).

OROS methylphenidate is an extended-release preparation of methylphenidate with an osmotic-release mechanism, which is thought to reduce the potential for abuse.[36] The efficacy

of this stimulant in 72 adults with ADHD was compared with that of placebo in 77 adults.[37] Over the 6 weeks of treatment with OROS methylphenidate, scores on the Adult ADHD Investigator Symptom Report Scale (AISRS) were significantly reduced, starting at week 3 ($p = .04$) and continuing to week 6 ($p < .001$).

Lisdexamfetamine, a therapeutically inactive prodrug that releases over 8 hours and has an absorption rate between immediate- and extended-release formulations of amphetamine products, was approved by the FDA in 2007 for use in children with ADHD. Two well-designed studies of lisdexamfetamine in children[38,39] produced improvements in ADHD symptoms compared with placebo. In 2008, FDA approval was given for lisdexamfetamine use in adults with ADHD. Unpublished data for lisdexamfetamine use in adults with ADHD were presented at the 54th annual meeting of the American Academy of Child and Adolescent Psychiatry.[40]

Dr. Adler stressed that any agent that has therapeutic effects can also have side effects. Common side effects of methylphenidate and amphetamine stimulants include dry mouth, insomnia, appetite suppression, headache, and a general sense of edginess.

Patients with ADHD may have difficulty with sleep prior to beginning stimulant therapy, and sometimes stimulant therapy can exacerbate sleep difficulties. Occasionally, stimulant medications will uncover a motor or vocal tic. The FDA has placed warnings on all approved stimulant and nonstimulant ADHD medications regarding the need for careful monitoring in patients with preexisting cardiovascular conditions because all of these agents can cause modest changes in blood pressure and heart rate; however, some patients may have greater changes. Finally, these agents must also be monitored for abuse or misuse.

Nonstimulants. Next, Dr. Adler discussed a large registration study[41] for atomoxetine involved 2 identical multisite, randomized, placebo-controlled trials with a total of 536 adults. The most frequently prescribed dose of atomoxetine was 90 mg/day. After 10 weeks of treatment, CAARS investigator-rated total scores showed significant effects of atomoxetine over placebo in both trials ($p = .005$ and $p = .002$).

Side effects that were observed more commonly with atomoxetine than with placebo included dry mouth, insomnia, nausea, decreased appetite, constipation, decreased libido, erectile difficulty, and dizziness.[41] Modest increases in blood pressure and heart rate were also observed.

Nonpharmacologic Treatment for ADHD

Dr. Adler explained that nonpharmacologic treatments can be important in adults with ADHD. Safren and colleagues[42] examined the use of cognitive-behavioral therapy (CBT) in adults with ADHD who were partially responsive to medication. Ongoing medication alone was compared with medication plus CBT. Patients who received CBT plus ongoing medication had less depression and anxiety and were more likely to be responders (56% versus 13% of the medication alone group, $p < .02$). For patients who have not completely responded to a pharmacologic intervention, CBT could be an effective augmentation strategy.

Pharmacotherapy for ADHD With a Comorbid Mental Health Disorder

Dr. Adler stated that in general, few data are available on the treatment of ADHD and comorbidities, and in some instances, the only data available are from studies in children and adolescents.

When patients have ADHD and a comorbid disorder, clinicians have to decide which disorder to target first. The general rule is to treat the most impairing disorder first. For example, if a patient has ADHD and MDD with suicidal ideation, the clinician would treat the depression first because of its acuity; although ADHD can be impairing, it is a lifelong disorder and may present less of an acute concern than the depression.

Substance use disorders. The risk of exacerbating SUD in ADHD patients by treating them with stimulants was recently reviewed. Wilens[27] stated that although childhood ADHD is a risk factor for adult SUD, stimulant treatment reduces the risk for cigarette smoking and SUD in adulthood. Wilens[27] recommended that, when treating a patient with active SUD, the clinician allow for 1 week to 1 month of abstinence before assessing ADHD symptomatology. Dr. Adler stressed that stimulants carry warnings regarding abuse liability.

A naturalistic observation[43] of treatment with bupropion sustained-release (SR) was conducted in 14 adolescents with ADHD who also had SUD and mood disorders. The researchers found improvement in major depression and reduction in drug use and ADHD symptomatology. An open-label investigation[44] of 13 nondepressed adolescents with ADHD, conduct disorder, and SUDs found significant improvement in ADHD symptoms after 5 weeks of treatment with bupropion, up to a dose of 300 mg/day (mean Clinical Global Impressions Severity of Illness decline, $p < .002$).

A 3-month, double-blind, placebo-controlled study[45] of atomoxetine in adults with ADHD and SUD showed significant effects from baseline ($p < .001$) of atomoxetine for ADHD. Patients with ADHD who had become abstinent from alcohol 4 to 30 days earlier were treated with atomoxetine or placebo for 12 weeks. Patients taking atomoxetine had significantly reduced ADHD symptoms as measured by the AISRS total score versus placebo ($p = .007$). Although the groups did not differ in time to relapse of heavy drinking, the patients taking atomoxetine had a 26% reduction in cumulative heavy drinking days.

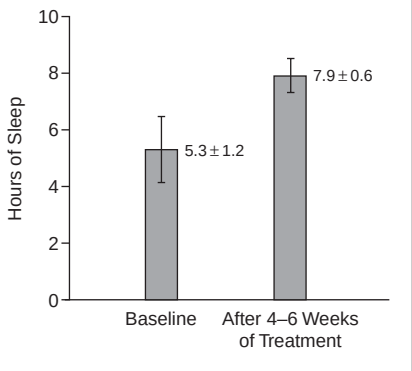
Mood disorders. Treatment with a combination of fluoxetine and methylphenidate was found to be effective in an 8-week open study[46] of 32 children and adolescents with ADHD and MDD

Table 4. Measures Before and After Fluoxetine Augmentation of Methylphenidate Treatment in Children and Adolescents (N = 32) With ADHD and Comorbid Depressive Disorder[a]

	Assessment Before Augmentation Treatment		Assessment After 8 Weeks of Augmentation Treatment		
Measure	Mean	SD	Mean	SD	p Value
C-GAS	44	6	60	6	< .0001
CDI	22	9	8	4	< .0001
CPRS-48					
Conduct	79	16	58	12	< .0001
Learning	84	10	64	10	< .0001
Psychosomatic	61	18	54	13	< .1071
Impulsive	70	15	53	14	< .0001
Anxiety	63	12	54	11	< .0010
Hyperactivity Index	81	11	59	10	< .0001
Grade-point averages	1.6	0.65	2.6	0.5	< .0001

[a]Adapted with permission from Gammon and Brown.[46]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CDI = Children's Depression Inventory, C-GAS = Children's Global Assessment Scale, CPRS-48 = Conners Parents Rating Scales.

Figure 3. Mean Hours of Sleep With Adjunctive Mirtazapine From a Chart Review of 14 Patients Aged 12 to 47 Years With ADHD and Stimulant-Associated Insomnia[a]



[a]Data from Adler et al.[52]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

or dysthymia who had not shown adequate response to methylphenidate alone (Table 4). Further, a naturalistic study[47] of 7 adolescents and 4 adults with ADHD and MDD found that a combination of fluoxetine or sertraline with a variety of different psychostimulants was effective for these comorbid disorders. The researchers noted that the antidepressants did not seem to improve the ADHD symptoms and the stimulants did not seem to improve the depressive symptoms. Although not an antidepressant, the norepinephrine reuptake inhibitor atomoxetine was recently found to improve ADHD but not depression ratings compared with placebo in 142 adolescents with ADHD and major depression.[48]

Few data are available for treating ADHD and comorbid bipolar disorder in adults. One study[49] of adolescents and children found that after bipolar symptoms were stabilized with divalproex, adjunctive mixed amphetamine salts could be used to treat the comorbid ADHD symptoms.

Anxiety disorders. Dr. Adler reported that data are lacking for the treatment of adult ADHD with comorbid anxiety disorders. However, in patients 8 to 17 years of age who had ADHD and anxiety disorders, a 12-week study[50] showed significant improvement in both anxiety symptoms ($p = .011$) and ADHD symptoms ($p < .001$) with atomoxetine versus placebo.

Sleep disorders. Dr. Adler stated that the use of α_2-agonists in children who have both ADHD and sleep disorders has been studied,[51] but few data exist for adults. A chart review[52] (Figure 3) of 14 patients aged 12 to 47 years with ADHD and stimulant-associated insomnia found significantly ($p < .0001$) reduced insomnia in those treated with adjunctive mirtazapine. A multicenter trial of an extended release version of the α_2-agonist guanfacine (2–4 mg/day) showed significant improvement in ADHD symptoms versus placebo in 345 children and adolescents with ADHD but without pre-existing sleep disorders (2 mg, $p = .0002$; 3–4 mg, $p = .0001$).[53]

Conclusion

Dr. Adler concluded that stimulant and nonstimulant medications are effective for ADHD in adults and generally well tolerated, but patients should be monitored for cardiovascular effects and, with some stimulants, misuse or abuse. Some data show efficacy for CBT augmentation for patients with ADHD who do not fully respond to medication therapy. Other data show efficacy of pharmacotherapy for comorbid psychiatric disorders in patients with ADHD. In some instances, clinicians may need to treat the comorbid psychiatric condition before treating ADHD.

Drug names: amphetamine/dextroamphetamine (Adderall and others), atomoxetine (Strattera), bupropion (Wellbutrin, Aplenzin, and others), dexmethylphenidate (Focalin and others), divalproex (Depakote), fluoxetine (Prozac and others), guanfacine (Tenex and others), lisdexamfetamine (Vyvanse), methylphenidate (Ritalin, Concerta, and others), mirtazapine (Remeron and others), sertraline (Zoloft and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, amphetamine/dextroamphetamine, bupropion, dexmethylphenidate, and methylphenidate are not approved by the U.S. Food and Drug Administration for the treatment of adult attention deficit-hyperactivity disorder (ADHD); atomoxetine is not approved for the treatment of childhood anxiety disorders, major depression, and ADHD; divalproex is not approved for the treatment of ADHD and bipolar disorder; fluoxetine is not approved for the treatment of ADHD and major depression/dysthymia; mirtazapine is not approved for the treatment of insomnia; sertraline is not approved for the treatment of ADHD and major depression; and guanfacine is not approved for the treatment of childhood ADHD.

REFERENCES

1. 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
2. Fayyad J, De Graaf R, Kessler R, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 2007;190:402–409
3. Barkley RA. Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2002;63(suppl 12):10–15
4. Biederman J, Faraone SV, Spencer TJ, et al. Functional impairments in adults with self-reports of diagnosed ADHD: a controlled study of 1001 adults in the community.

J Clin Psychiatry 2006;67:524–540
5. Barkley RA, Murphy KR, Fischer M. ADHD in Adults: What the Science Says. New York, NY: Guilford Press; 2008
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
7. Weyandt LL, Iwaszuk W, Fulton K, et al. The Internal Restlessness Scale: performance of college students with and without ADHD. J Learn Disabil 2003;36:382–389
8. Barkley RA. Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment. 3rd ed. New York, NY: Guilford Press; 2005
9. Murphy K, Barkley RA. Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. Compr Psychiatry 1996;37: 393–401
10. Stavro GM, Ettenhofer ML, Nigg JT. Executive functions and adaptive functioning in young adult attention-deficit/hyperactivity disorder. J Int Neuropsychol Soc 2007;13:324–334
11. McGough JJ, Barkley RA. Diagnostic controversies in adult attention deficit hyperactivity disorder. Am J Psychiatry 2004;161:1948–1956
12. Conners CK, Erhart D, Sparrow E. Conners' Adult ADHD Rating Scales, Technical Manual. New York, NY: Multi-Health Systems; 1999
13. The Americans With Disabilities Act of 1990. Available at http://www.ada.gov/pubs/ada.htm. Accessed Apr 9, 2008
14. Barkley RA. Driving impairments in teens and adults with attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2004;27:233–260
15. Carlson CL, Mann M. Sluggish cognitive tempo predicts a different pattern of impairment in the attention deficit hyperactivity disorder, predominantly inattentive type. J Clin Child Adolesc Psychol 2002;31:123–129
16. Kent L, Craddock N. Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? J Affect Disord 2003;73: 211–221
17. Faraone SV, Biederman J. Do attention deficit hyperactivity disorder and major depression share familial risk factors? J Nerv Ment Dis 1997;185:533–541
18. Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 1993;150:1792–1798
19. Seager MC, O'Brien G. Attention deficit hyperactivity disorder: review of ADHD in learning disability: the Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities/Mental Retardation [DC-LD] criteria for diagnosis. J Intellect Disabil Res 2003;47(suppl 1):26–31
20. Rey JM, Morris-Yates A, Singh M, et al. Continuities between psychiatric disorders in adolescents and personality disorders in young adults. Am J Psychiatry 1995;152:895–900
21. Barkley RA, Fischer M, Smallish L, et al. Young adult follow-up of hyperactive children: antisocial activities and drug use. J Child Psychol Psychiatry 2004;45:195–211
22. Fossati A, Novella L, Donati D, et al. History of childhood attention deficit/hyperactivity disorder symptoms and borderline personality disorder: a controlled study. Compr Psychiatry 2002;43: 369–377
23. Wilens TE, Biederman J, Mick E, et al. Attention deficit hyperactivity disorder (ADHD) is associated with early onset substance use disorders. J Nerv Ment Dis 1997;185:475–482
24. Biederman J, Monteaux MC, Spencer T, et al. Stimulant therapy and risk for subsequent substance use disorders in male adults with ADHD: a naturalistic controlled 10-year follow-up study. Am J Psychiatry 2008;165:597–603
25. Barkley RA, Fischer M, Smallish L, et al. Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? a 13-year prospective study. Pediatrics 2003;111:97–109
26. Wilens TE, Faraone SV, Biederman J, et al. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? a meta-analytic review of the literature. Pediatrics 2003;111:179–185
27. Wilens TE. The nature of the relationship between attention-deficit/hyperactivity disorder and substance use. J Clin Psychiatry 2007; 68(suppl 11):4–8
28. Levin ED, Rezvani AH. Nicotinic treatment for cognitive dysfunction. Curr Drug Targets CNS Neurol Disord 2002;1:423–431
29. McCann BS, Roy-Byrne P. Attention-deficit/hyperactivity disorder and learning disabilities in adults. Semin Clin Neuropsychiatry 2000;5: 191–197
30. Miller CJ, Miller SR, Newcorn JH, et al. Personality characteristics associated with persistent ADHD in late adolescence. J Abnorm Child Psychol 2008;36:165–173
31. Spencer TJ, Biederman J, Wilens T. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:456–463
32. Spencer T, Biederman J, Wilens T, et al. Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2001;58:775–782
33. Weisler RH, Biederman J, Spencer TJ, et al. Mixed amphetamine salts extended-release in the treatment of adult ADHD: a randomized, controlled trial. CNS Spectr 2006;11:625–639
34. Adderall XR [package insert]. Wayne, Pa: Shire US Inc; 2007. Available at: http://www.adderallxr.com/assets/pdf/prescribing_information.pdf. Accessed Feb 28, 2008
35. Spencer TJ, Adler LA, McGough JJ, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2007;61:1380–1387
36. Spencer TJ, Biederman J, Ciccone PE, et al. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. Am J Psychiatry 2006;163:387–395
37. 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. Correction 2007;61:1402
38. Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther 2007;29:450–463
39. Biederman J, Boellner SW, Childress A, et al. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry 2007;62:970–976
40. Adler LA, Goodman DW, Kollins SH, et al. Efficacy and safety of lisdexamfetamine dimesylate in adults with attention deficit hyperactivity disorder [poster]. Presented at the 54th annual meeting of the American Academy of Child and Adolescent Psychiatry; October 23–28, 2007; Boston, Mass
41. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biol Psychiatry 2003;53:112–120
42. Safren SA, Otto MW, Sprich S, et al. Cognitive-behavioral therapy for ADHD in medication-treated adults with continued symptoms. Behav Res Ther 2005;43:831–842
43. Solhkhah R, Wilens TE, Daly J, et al. Bupropion SR for the treatment of substance-abusing outpatient adolescents with attention-deficit/hyperactivity disorder and mood disorders. J Child Adolesc Psychopharmacol 2005;15: 777–786
44. Riggs PD, Leon SL, Mikulich SK, et al. An open trial of bupropion for ADHD in adolescents with substance use disorders and conduct disorder. J Am Acad Child Adolesc Psychiatry 1998;37: 1271–1278
45. Wilens TE, Adler LA, Weiss MD, et al. Atomoxetine treatment of adults with ADHD and comorbid alcohol use disorders [published online ahead of print Apr 9, 2008]. Drug Alcohol Depend 2008;96:145–154. doi: 10.1016/j.drugalcdep.2008.02.009
46. Gammon GD, Brown TE. Fluoxetine and methylphenidate in combination for treatment of attention deficit disorder and comorbid depressive disorder. J Child and Adolesc Psychopharmacology 1993;3:1–10
47. Findling RL. Open-label treatment of comorbid depression and attentional disorders with co-administration of serotonin reuptake inhibitors and psychostimulants in children, adolescents, and adults: a case series. J Child Adolesc Psychopharmacol 1996;6:165–175
48. 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;17:407–420
49. Scheffer RE, Kowatch RA, Carmody T, et al. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. Am J Psychiatry 2005;162:58–64
50. Geller D, Donnelly C, Lopez F, et al. Atomoxetine treatment for pediatric patients with attention-deficit/hyperactivity disorder with comorbid anxiety disorder. J Am Acad Child Adolesc Psychiatry 2007;46:1119–1127
51. Prince JB, Wilens TE, Biederman J, et al. Clonidine for sleep disturbances associated with attention-deficit hyperactivity disorder: a systematic chart review of 62 cases. J Am Acad Child Adolesc Psychiatry 1996;35:599–605
52. Adler LA, Reingold LS, Morrill MS, et al. Combination pharmacotherapy for adult ADHD. Curr Psychiatry Rep 2006;8:409–415
53. Biederman J, Melmed RD, Patel A, et al. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics 2008;121:e73–84

For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 1344–1346.

