Managing ADHD in Children, Adolescents, and Adults With Comorbid Anxiety

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the teleconference roundtable "Managing ADHD in Children, Adolescents, and Adults With Comorbid Anxiety," which was held September 15, 2006. 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 teleconference roundtable was chaired by ***Lenard A. Adler****, M.D., Departments of Psychiatry and Neurology, 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;* ***Jeffrey H. Newcorn****, M.D., Department of Psychiatry and the Division of Child and Adolescent Psychiatry, Mt. Sinai School of Medicine, New York, N.Y.;* ***Thomas J. Spencer****, M.D., Department of Psychiatry, Harvard Medical School and Department of Pediatric Psychopharmacology, Massachusetts General Hospital, Boston; and* ***Margaret D. Weiss****, M.D., Ph.D., Department of Psychiatry, University of British Columbia and the Provincial ADHD Program, Children's and Women's Health Centre of British Columbia, Vancouver, Canada.*

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Introduction

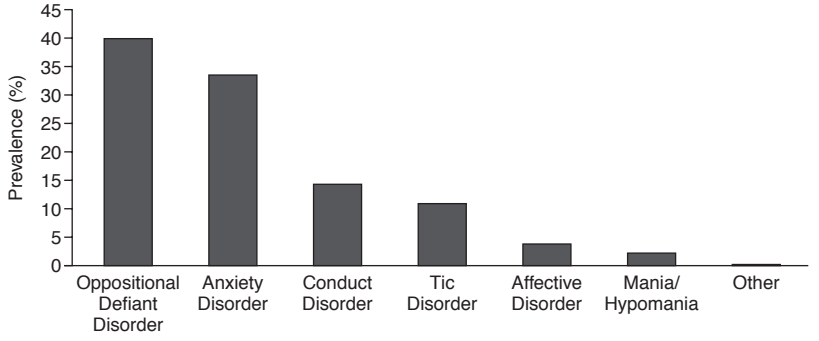
Attention-deficit/hyperactivity disorder (ADHD) is a relatively common disorder, estimated to affect 3% to 6% of children[1] and 4.5% of adults.[2] Individuals with ADHD, their families, and society as a whole bear the burden of this disorder, even though effective pharmacologic and psychosocial treatments are available. Annual direct medical costs for children with ADHD have been found to be approximately 50% to 75% more than those of children without ADHD,[3,4] and family members of patients with ADHD have direct and indirect costs that are almost double those of family members of children without ADHD.[4] Furthermore, ADHD is associated with poor educational outcomes, including low grades at school and low scores on standardized tests.[5] Adolescents with ADHD are more likely to drop out of high school than those without ADHD (32%–38% vs. 5%).[6,7] In addition, adolescents and young adults with ADHD are more likely to be cited for speeding, have driver's licenses suspended, be involved in crashes, and have unsafe driving habits such as erratic steering, false braking, and slow reaction times.[8]

Adult ADHD is also correlated with a heavy social burden.[9] Parents of children with ADHD who had ADHD themselves were less likely to have a college degree and thus more likely to be unskilled workers than adults who did not have ADHD. In addition, the rate of lifetime comorbidity with other psychiatric disorders was higher in parents with ADHD than in those without.

The rate of comorbid disorders in children with ADHD is high as well. The Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA) Cooperative Group[10] found that at baseline 69% of children with ADHD had another psychiatric disorder, 2 of the most frequent being oppositional defiant disorder and anxiety disorders (Figure 1).[10] The presence of these comorbid disorders can complicate making an accurate diagnosis and selecting the most appropriate treatments for ADHD. Although pharmacotherapy is a first-line, evidence-based treatment for ADHD, there has been some question as to whether stimulant treatment is equally effective in patients with ADHD and these comorbid conditions.[11] Additional treatment targeted at the comorbid disorder is often required.

The American Academy of Pediatrics[12] and the American Academy of Child and Adolescent Psychiatry[13] have both published detailed treatment guidelines to assist physicians in diagnosing and managing ADHD. Despite these guidelines, studies[14,15] have shown that a high degree of variability exists in physicians' treatment practices. Since ADHD is treated by a variety of medical and nonmedical professionals, the treatment practices and knowledge base of the different treatment providers are likely to vary. In addition, a variety of other factors are likely to affect physician approaches to treatment, including information or public opinion pieces regarding ADHD in the media, the rapid rate in which new information is published in the medical literature, the large number of journals and other resources in which this information can be found, and physician and patient attitudes regarding the condition and its treatment. Since the presence of a comorbid condition

Figure 1. Prevalence of Comorbidity in the MTA Sample of Children With ADHD at Baseline[a]



[a]Data from the MTA Cooperative Group.[10]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, MTA = Multimodal Treatment Study of Children With ADHD.

such as anxiety may affect the use of established treatments and alter the standard recommendations for the evaluation and treatment of ADHD, an expert panel of clinician/researchers was convened for a teleconference to offer practical guidance regarding diagnosis and treatment of ADHD in children, adolescents, and adults with comorbid anxiety and anxiety disorders.

Epidemiology of Comorbid Anxiety Disorders in Patients With ADHD

To begin the discussion, Lenard A. Adler, M.D., asked the group to describe the prevalence of comorbid anxiety in patients with ADHD, as well as the types of anxiety disorders that often co-occur with this disorder.

Children and Adolescents

Russell A. Barkley, Ph.D., stated that 33.5% of the 579 children with ADHD (aged 7–9.9 years at study entry) who participated in the MTA study had a comorbid anxiety disorder.[10] According to a review by Biederman et al.,[16] epidemiologic and clinical samples of children with anxiety disorders and children with ADHD exhibited a comorbid association between the 2 disorders of about 25%. Clearly, the conditions co-occur frequently, although the exact percentages likely vary according to the sample studied and mode of assessment utilized.

Many types of anxiety disorders have been found to be present in children with ADHD, including separation anxiety, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD).[17] Further, children and adolescents with panic disorder and agoraphobia have also been found to have high rates of ADHD.[18]

Some variability occurs with gender and age. Thomas J. Spencer, M.D., noted that a review from Massachusetts General Hospital[19] examined the effects of gender on ADHD and comorbid anxiety. Data[20] showed that 33% of girls with ADHD and 28% of boys with ADHD between the ages of 6 and 19 years had at least 2 comorbid anxiety disorders. Although no significant differences in anxiety comorbidity rates were found between the genders, the subgroups of anxiety disorders did differ between girls and boys with ADHD (Table 1).[20] Girls with ADHD had a greater prevalence of simple phobia, agoraphobia, and panic disorder than boys with ADHD.

Dr. Spencer acknowledged that referred samples are often thought to have a higher prevalence of comorbid disorders than those who are not referred for treatment. However, a review by Angold et al.[21] showed that untreated children and adolescents with ADHD in the community also had high prevalence rates of anxiety compared with children and adolescents without ADHD (12.8%–50.8% vs.1%–14.6%, respectively).

The comorbidity rate of anxiety disorders and ADHD increases over time, from approximately 25% of children[16] to over one third of adolescents and even higher in adults.[17] For example, one report[22] found a higher rate of anxiety disorders in children with ADHD after 4 years (35%) compared with baseline (27%) and rates in non-ADHD controls (5% at baseline and 9% at 4-year follow-up). Dr. Barkley noted that longitudinal studies[23] have suggested that children with ADHD who went on to develop anxiety disorders as adults typically had higher rates of simple phobias in the preschool years than the general population. Dr. Barkley suggested that simple phobias seem to pose a risk for separation anxiety and social phobia upon entering school, and if these anxieties in young children with ADHD persist into mid- to late childhood, they may blossom into general anxiety disorder.

Dr. Spencer agreed and said that panic disorder with and without agoraphobia or OCD tends to progress longitudinally in a pure form, although these disorders may take the form of other anxiety disorders as the patient matures. Even within families, anxiety disorders may manifest differently in individuals. Dr. Barkley elaborated that 40% of the variance in anxiety is genetic,[24] and explained that the incidence of anxiety is greater within families of patients with anxiety. Similarly, Biederman et al.[25] found that the risk of multiple anxiety disorders was higher in first-degree relatives of patients with ADHD compared with relatives of children in the control group.

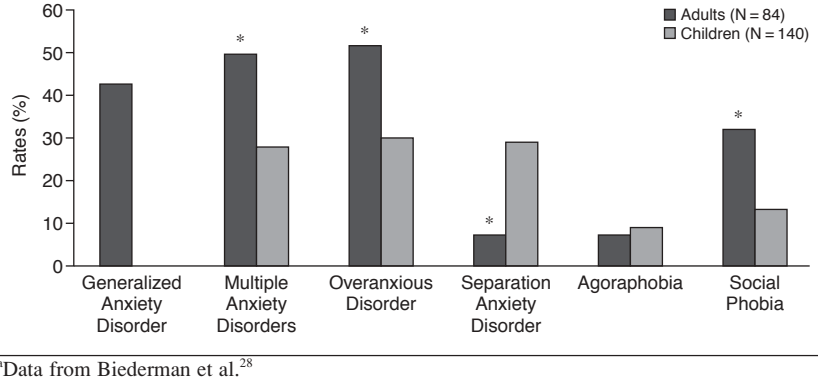
Dr. Spencer stated that the results from the Yale Family Study[26] revealed a highly specific genetic risk for anxiety disorder; children's diagnoses were predicted by the parents' diagnoses. For example, children of probands with depression and no anxiety disorder did not present with anxiety disorders, whereas children of probands with

Table 1. Gender Differences in the Prevalence of ≥ 2 Comorbid Anxiety Disorders in Children With ADHD[a]

	Girls		Boys	
Comorbidity	With ADHD (N = 140) N (%)	Without ADHD (N = 120) N (%)	With ADHD (N = 140) N (%)	Without ADHD (N = 122) N (%)
Simple phobia	40 (29)	13 (11)	26 (19)	6 (5)
Social phobia	20 (14)	4 (3)	18 (13)	4 (3)
Agoraphobia	22 (16)	3 (3)	13 (9)	2 (2)
Panic disorder	7 (10)	1 (1)	1 (1)	0 (0)
Separation anxiety	36 (26)	12 (10)	40 (29)	6 (5)
Overanxious disorder	40 (29)	2 (2)	42 (30)	8 (7)

[a]Data from Biederman et al.[20]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 2. Rates of Comorbid Disorders in Clinically Referred Children and Adults With ADHD[a]



[a]Data from Biederman et al.[28]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.
*p ≤ .01 vs. children with ADHD.

depression and panic disorder had a high prevalence of any anxiety disorder (36.8%). Further, the presence of any anxiety disorder in parents increased the risk of anxiety disorders in the children.

Adults

Next, Dr. Adler inquired about the epidemiology of comorbid ADHD a nd anxiety in adults. Dr. Barkley cited findings from one study[9] in which the rate of lifetime comorbidity with other psychiatric disorders was higher in adults with ADHD than in those without ADHD. In this study,[9] 87% of parents of children with ADHD who had ADHD themselves had at least 1 other psychiatric disorder and 56% of those with ADHD had at least 2 comorbid psychiatric disorders versus 64% and 27%, respectively, of those without ADHD. A significant difference (p = .0001) existed in the number of anxiety disorders between parents with ADHD (21%) and parents without ADHD (8%).[9] According to the National Comorbidity Survey Replication (NCS-R),[27] 47.7% of adults with ADHD had a comorbid anxiety disorder compared with 19.5% of adults without ADHD. Social phobia (29.3%), specific phobia (22.7%), and PTSD (11.9%) were the most common anxiety subgroups found in adults with ADHD.

In a cross-sectional study by Biederman et al.,[28] 50% of referred adults with ADHD had multiple anxiety disorders compared with 42% of nonreferred adults with ADHD and 28% of referred children with ADHD. Dr. Adler pointed out that these prevalence rates are similar to the rates reported in the NCS-R study.[27] These studies found that referred and nonreferred groups of adults with ADHD had similar high rates of comorbid anxiety, which, the authors noted, suggests that the high rates of comorbid anxiety disorders in referred studies are not due to ascertainment bias. Dr. Barkley stated that the rates of comorbid anxiety disorders in adults with ADHD were higher than the rates found in children with ADHD.[10,28,29] As an explanation, Dr. Barkley suggested that self-referral in adults may increase the likelihood of an anxiety disorder diagnosis, whereas this phenomenon is not as apparent in children with ADHD. Concerning types of anxiety comorbidity,[28] Dr. Spencer observed that referred children with ADHD had higher rates of separation anxiety disorder while referred adults with ADHD had higher rates of social phobia (Figure 2).[28]

Dr. Adler asked if PTSD is more often comorbid in adults with ADHD than in children with ADHD; Dr. Spencer replied that the prevalence is dependent on being exposed to a setting in which one might encounter trauma, which may increase with age. Also, Dr. Spencer stated that while anxiety and ADHD are discrete, people with one type of disorder tend to have certain other comorbid disorders. Jeffrey Newcorn, M.D., agreed that certain disorders seem to occur in clusters or groupings. Dr. Barkley said that, in a recent study,[30] adults with ADHD who were also diagnosed with generalized anxiety disorder had substantially increased risks for major depression, dysthymia, and oppositional defiant disorder.

Clinical Presentation of ADHD and Comorbid Anxiety Disorders

Childhood anxiety disorders, according to Dr. Barkley, may be easily missed in that parents do not always realize that their children have internalizing symptoms. One study[31] found that half of children with ADHD who met criteria for overanxious disorder according to their own report were not described as anxious in parental interviews. In fact, self-reports, as opposed to parent reports, may more accurately

Table 2. Overlapping Cognitive and Behavioral Symptoms of ADHD and Anxiety in Children[a]

Cognitive
Rumination
Vigilant apprehension
Catastrophic thinking
Great embarrassment
Threat to life
Behavioral
Agitation
Tantrums
Attention-seeking
Overdependence
Rituals

[a]Based on Spencer.[36]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 3. Associated Symptoms of Adult ADHD[a]

Reactivity
Risk taking; inability to tolerate low stimulation
Environmental dependence
Procrastination
Inability to generate forced effort
Mood lability
Lack of motivation
Temper outbursts
Inept social skills or lack of social judgment
Poor frustration tolerance
Dysregulated sleep, nutrition, exercise, health

[a]Reprinted with permission from Weiss and Weiss.[37]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

identify symptoms of anxiety in children with ADHD.[31] Therefore, interviewing the child is important in detecting this particular comorbid condition.

Dr. Barkley stated that children and adolescents who present with ADHD and anxiety symptoms have a great deal of personal and family distress, and have often experienced emotionally traumatic events. These individuals also have a higher risk of being bullied, especially the more anxious and physically smaller they are. In fact, Dr. Barkley pointed out that bullying, as well as physical or sexual abuse, might be the primary reason treatment was sought for the child,[32] as opposed to the symptoms of ADHD, which might be a secondary complaint. Additionally, the risk of having been bullied or abused is elevated in children with ADHD.[33,34]

Anxiety disorder symptoms in children often resemble those seen in adults, except for separation anxiety disorder and selective mutism, which are more specific to childhood.[35] In children, cognitive and behavioral features of anxiety can be misinterpreted because they overlap with ADHD symptoms (Table 2).[36] Overactive children are not usually diagnosed with anxiety disorders, just as inhibited children are not usually suspected of having ADHD.

Margaret D. Weiss, M.D., Ph.D., stated that somatic symptoms, restlessness, and irritability often overlap in ADHD and anxiety disorders, but other symptoms tend to be more specific to anxiety, such as obsessive-compulsive symptoms, worry about things that are unlikely to occur, and specific phobias. To determine the course of treatment, it may be helpful for the clinician to identify whether the symptom is associated with ADHD itself or specific to anxiety disorder per se—since the former group of anxiety symptoms may actually improve with treatment of ADHD.

Adults with ADHD and anxiety disorders may not seek treatment because of ADHD, and identifying the associated symptoms of ADHD can be problematic because these patients have lived with these symptoms all of their lives and may not recognize them as problematic (Table 3).[37] Acute mood and anxiety symptoms are more salient to the patient because of their novel and disruptive nature, increasing the likelihood that these symptoms will be the chief complaint.[37] For example, adults with social anxiety incessantly worry about embarrassing social situations, which tend to be an alienating problem, and may motivate patients to seek treatment. Dr. Weiss noted that in differentiating social anxiety disorder from consequences of ADHD itself, it may be useful to ask patients whether they avoid social situations because they have a long history of inappropriate social behaviors or they are overwhelmed by being with people irrespective of concerns about their behavior.

Dr. Spencer suggested that simply being aware of the possibility that anxiety can coexist with ADHD may help in the detection of these disorders. In the past, anxiety was thought to be an internalizing disorder and ADHD an externalizing condition. As a result, it was believed that anxiety was protective against ADHD; however, this has since been shown not to be the case. For example, epidemiologic studies uniformly show greater (not lesser) rates of comorbid internalizing disorders in the presence of externalizing disorders.[21] Dr. Spencer also noted that many patients may not exhibit anxious behavior in the calm, reassuring clinical setting. Therefore, asking about anxiety as part of the review of systems for patients with ADHD is important, instead of relying on patients to spontaneously report symptoms of anxiety.

Patients in real-world clinical practice often present with more than 2 disorders at a time. A review by Pliszka[38] showed that children with comorbid ADHD and anxiety had higher rates of conduct disorder, more reported school problems and social difficulties, with more stressful life events than children with only ADHD. According to Dr. Weiss, studies[39,40] have concluded that up to three fourths of patients with ADHD will have one or more clinically significant comorbid disorders. However, studies often examine ADHD and only one comorbid disorder at a time. They do not consider whether other disorders are present that require either independent treatment or if modified treatment is recommended. Anxiety symptoms are often present with the core symptoms of ADHD, which may indicate a significant level of impairment that will not respond to treatment of ADHD alone and should be assessed and adequately treated.

Subsyndromal Symptoms

Although many patients with ADHD have diagnoses of other disorders, some have comorbid symptoms that do not reach the threshold level for another diagnosis. Patients with ADHD often complain of symptoms such as low self-

esteem, temper outbursts, mood dysregulation, reactivity, anxiety, poor motivation, and other symptoms that are traditionally associated with disorders such as anxiety and depression. While these symptoms may be an important aspect of the clinical presentation, they may not meet the full diagnostic criteria for a mood or anxiety disorder. In a study of adult ADHD by Dr. Weiss and colleagues,[41] only 33% of the subjects met the full diagnostic criteria for mood or anxiety disorders as measured by the Structured Clinical Interview for the DSM-IV-TR (SCID), although a majority presented with clinically significant symptoms of anxiety and dysphoric mood associated with subjective impairment.

In addition, adults with conditions that are traditionally characterized as externalizing disorders in children (e.g., oppositional defiant or conduct disorders) can feel subjective distress, which may manifest as anxiety. Referring again to her 2006 study,[41] Dr. Weiss said that those individuals with ADHD who did not meet full criteria for anxiety were often aware that they were in danger of being late, procrastinating, or not meeting expectations and as a result became anxious. In addition, their anxiety further impaired their working memory, thereby worsening the symptoms of ADHD, which in turn fueled more anxiety, and thus perpetuated a vicious cycle of increasing ADHD and anxiety symptoms and associated impairments. The intertwining of problems with anxiety, executive function, and attention over the course of a lifetime can obscure the primary disorder.

Dr. Adler agreed that it is important to differentiate between a subjective sense of anxiety and the diagnostic criteria for an anxiety disorder in patients with ADHD. Scales that are specifically designed to measure anxiety disorders may not adequately measure feeling state symptoms. Dr. Weiss elaborated that in the aforementioned study,[41] the Hamilton Rating Scale for Anxiety (HAM-A) in fact did not detect feeling state symptoms, which were still functionally important and were a predictor of treatment outcome. Despite the fact that cognitive behavioral therapy (CBT) has been shown to be an effective intervention for anxiety, both the HAM-A and the Beck Anxiety Inventory measures of anxiety place greater emphasis on somatic symptoms than cognitive impairments such as worry and fear.

Pharmacologic Treatment of ADHD and Comorbid Anxiety Disorders

Dr. Adler suggested the group discuss the treatment paradigms for ADHD and comorbid anxiety disorders, first in younger patients and then in adults, including whether the anxiety or the ADHD should be treated first and whether to use stimulants, nonstimulants, antidepressants, or some combination of treatments.

Children and Adolescents

Stimulants. Dr. Newcorn stated that early studies[11,31,42–44] found that children with ADHD and comorbid anxiety disorders were less responsive to stimulant treatment and also had higher rates of side effects, including tics, than those without anxiety. Dr. Barkley noted that only 3 studies (one being the MTA)[45–47] found no connection between anxiety and stimulant response. However, these 3 studies were quite large and more recent. Dr. Newcorn pointed out that response rates for children with ADHD and comorbid anxiety varied in 2 cohorts from Toronto.[42,47] In the earlier double-blind, placebo-controlled study,[42] 18 anxious and 22 nonanxious children with ADHD were randomly assigned to receive 1 of 3 doses of methylphenidate (0.3, 0.6, or 0.9 mg/kg/day). Methylphenidate reduced activity levels in both groups of children but improved working memory only in the nonanxious group across all treatment conditions. The low dose (0.3 mg/kg/day) produced an increase in heart rate among the anxious group, but no other differential drug effects existed between the two groups. The later study by Diamond et al.[47] assessed primarily behavioral measures in response to methylphenidate in children with ADHD (53 without comorbid anxiety and 38 with comorbid anxiety) titrated to a dose of 0.7 mg/kg b.i.d. Although the group with comorbid anxiety had more physical symptoms at baseline, there was no difference in drug effects overall between the 2 groups. The results found no difference in methylphenidate response in the presence of comorbid anxiety. In the MTA study,[45] comorbid anxiety did not specifically affect response to medication treatment. The anxious and nonanxious subgroups of patients with ADHD in this study had similar rates of improvement on medication treatment. However, comorbid anxiety did moderate response to behavioral therapy administered alone in the MTA study. The group who did not receive medication had a better response to the behavioral therapy in the presence of comorbid anxiety than did the group without comorbid anxiety.

Dr. Barkley stressed that the data regarding the effects of comorbid anxiety on stimulant treatment are still inconclusive, and suggested that the degree of effect could be associated with the type of anxiety disorder present in the patient. Dr. Weiss noted that both ADHD and anxiety tend to be longstanding developmental disorders, and variance in response may depend on the patients' difficulties at the time they present for help. Dr. Newcorn added that another possible area of importance is comorbidity with other disorders. As noted earlier, patients in real-world clinical practice often present with more than 2 disorders at a time. A patient who has ADHD, anxiety disorders, and disruptive disorders, for example, will have a somewhat different clinical presentation, and may respond differently to a treatment than a patient with ADHD, anxiety disorder, and, say, a tic disorder. Examining these combinations, Dr. Newcorn sug-

gested, could provide an opportunity to understand differences in outcomes between patients. Dr. Barkley hypothesized that study discrepancies could be due to the types of anxiety scales used; some studies used dimensional rating scales such as the Child Behavioral Checklist, while others used DSM-based diagnoses.

Dr. Weiss listed 4 methodological issues that reflect real-world clinical practice and should be considered in future research on ADHD and comorbid anxiety treatment. In order to develop a research methodology that can provide meaningful evidence on management of ADHD and anxiety, several innovations are required. First, it is necessary to distinguish symptoms common to both disorders from symptoms unique to only one disorder. For example, improvement in restlessness and tension in management of ADHD may represent a secondary gain of improvement in ADHD itself rather than improvement in a specific anxiety disorder. Second, it is necessary to determine the extent to which remission of one disorder will drive improvement in the other. For example, a patient with severe GAD who is constantly worried and responds fully to an SSRI may no longer experience problems with forgetfulness or attention. Third, rating scales are needed for anxiety that emphasize cognitions that form the hallmark of the disorder, are not present in ADHD, and are not common side effects of treatment. The essence of GAD is worry, of phobia is fear, of PTSD is terror, and of OCD is intolerance of uncertainty. With scales that emphasize sleep, headache, gastrointestinal complaints, and other generic problems, it is difficult to distinguish whether the improvement brought about by treatment is pathognomonic. Anxiety scales that do not include associated symptoms of ADHD and generic physical problems are essential to determine whether treatments are affecting one disorder or both. Lastly, research in comorbid ADHD and anxiety requires a broader view of outcome than looking at treatment response in symptoms for each disorder alone. Discrepancies in previous research are often based on looking at very different outcomes. Studies that look at whether treatment is as easily tolerated, whether it is possible to treat ADHD in patients with anxiety, or whether neuropsychological testing outcomes are comparable in ADHD versus ADHD/anxiety all focus on very different issues. Dr. Newcorn commented that successful treatment of ADHD can make children feel more confident in performance situations—whether social or academic—making it difficult to distinguish treatment effects on bona fide anxiety symptoms from the ameliorating effects on ADHD.

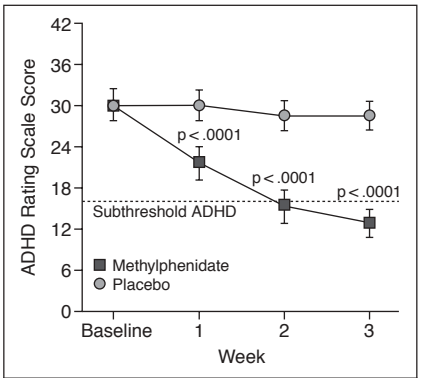
Because there is no definitive answer to whether stimulants improve anxiety disorders, whether anxiety disorders worsen response to stimulant treatment for ADHD, or whether there is no impact on the treatment as a function of comorbidity, Dr. Barkley recommended using caution when prescribing stimulant medication to children with ADHD who have comorbid anxiety. However, other discussants, reflecting the more recent, large-scale studies that indicate no difference in response or tolerability as a function of comorbid anxiety, indicated that it is appropriate to treat with stimulants and change treatment if the response is not adequate or problems arise.

Nonstimulants. Dr. Adler moved the discussion toward the use of nonstimulants in children and adolescents. Dr. Barkley cited a randomized, placebo-controlled study[48] of children with ADHD and comorbid anxiety disorders that showed some improvement in anxiety symptoms after treatment with atomoxetine (a selective norepinephrine reuptake inhibitor [SNRI] approved for the treatment of ADHD). Dr. Newcorn mentioned that in this study, the effect size for anxiety symptom reduction was about 0.5, which was about half that for ADHD. Dr. Newcorn hypothesized that the large effect size for ADHD in the presence of comorbid anxiety, coupled with a moderate effect on anxiety, might suggest an even more robust effect of atomoxetine in children with ADHD and comorbid anxiety disorders than in children with only ADHD or ADHD and a different comorbidity. However, there are not yet studies which directly compare response to atomoxetine in these various comorbid groups.

Drug combinations. Dr. Adler stressed that in clinical practice, if a patient with ADHD has a robust anxiety disorder, combination treatment is often appropriate. Dr. Spencer pointed out that, fortunately, no pharmacokinetic interactions exist between the agents that are typically used for anxiety, such as most selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, buspirone, and the stimulants or nonstimulants that are used in ADHD treatment; however, Dr. Adler added that there is an interaction between atomoxetine and the SSRIs fluoxetine and paroxetine secondary to cytochrome P450 2D6 (CYP4502D6) interactions.

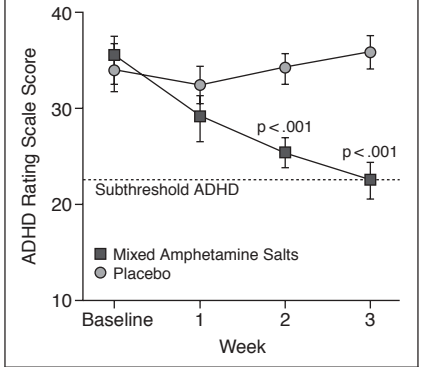
Abikoff et al.[46] for the Research Units on Pediatric Pharmacology (RUPP) ADHD/Anxiety Study Group conducted a study that addressed treatment of children with both ADHD and anxiety disorders, which Dr. Spencer commented was noteworthy because most studies enroll patients who have only one disorder. Subjects were first treated with methylphenidate, and then either placebo (N = 10) or the SSRI fluvoxamine (N = 15) was added. No significant difference was found in the response to stimulant treatment between patients with ADHD and comorbid anxiety and those with ADHD only. In some patients, the anxiety symptoms persisted and might warrant treatment; however, the benefit of fluvoxamine augmentation was not apparent in this study. This replicates the finding in Weiss et al.,[41] in which the combination of paroxetine and dextroamphetamine led to no greater improvement in the clinician rating of global treatment than a single treatment. Dr. Spencer noted that although the sample size was small, the results of this study suggest that anxiety symp-

Figure 3. ADHD Rating Scale Scores With Methylphenidate Versus Placebo in Adults With ADHD[a]



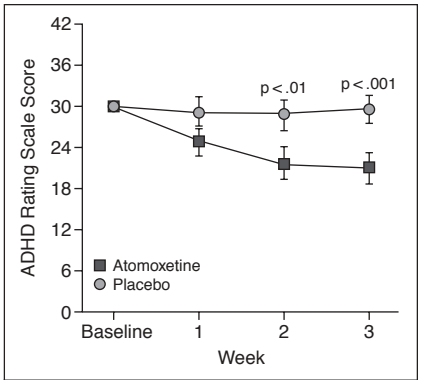
[a]Reprinted with permission from Spencer et al.[52]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 4. Mixed Amphetamine Salts Versus Placebo for ADHD in Adults[a]



[a]Reprinted with permission from Spencer et al.[53]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 5. ADHD Rating Scale Scores With Atomoxetine Versus Placebo in Adults With ADHD[a]



[a]Reprinted with permission from Spencer et al.[54]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

toms may persist despite successful stimulant treatment of ADHD.

Kratochvil et al.[49] tested the nonstimulant atomoxetine and the SSRI fluoxetine in children with ADHD and comorbid anxious or depressive symptoms. Subjects were randomized to receive either fluoxetine (N = 127) or placebo (N = 46) for 3 weeks, with atomoxetine added for 5 additional weeks. Both treatment groups experienced significant reductions in ADHD, anxiety, and depressive symptoms ($p < .001$). The 2 groups had similar completion rates and discontinuation rates for adverse events, although blood pressure and pulse rate were increased in the combination group. Although the atomoxetine and fluoxetine combination was well tolerated, atomoxetine monotherapy appeared to be just as effective. However, interpretation is made complex by the absence of a placebo control group.

Dr. Weiss commented that treatment of anxiety has been complicated in clinical practice. One of the most prominent difficulties became evident when the concern arose about SSRI-induced suicidality, and anxiety and depression were not treated as distinct disorders. A child who has a severe anxiety disorder is substantially impaired. The risk-benefit ratio of use of SSRIs in depression is relatively high in that response versus placebo is poor. However, the evidence on the efficacy of SSRIs for treatment of anxiety in children is robust, and the risk-benefit ratio lower. In areas where psychological treatments are not available, this may have lead to the undertreatment of severely impairing anxiety disorders in children.[50,51] Dr. Newcorn stressed that more data are needed, and commented that implementing a medication with certain risks would be easier to do if the indication of benefits in studies were more robust.

Adults

Dr. Adler observed that, while awareness of adult ADHD has increased, there are fewer data on the treatment of ADHD and comorbid anxiety for adults than children and adolescents. Dr. Spencer agreed that current information in this area is mostly anecdotal and must be extrapolated from studies in the ADHD-only population.

The results of controlled studies of pharmacologic treatments have been comparable for ADHD in children, adolescents, and adults. Dr. Spencer and his colleagues conducted several randomized, placebo-controlled, crossover studies[52–53] assessing the pharmacotherapeutic value of different medications to treat ADHD. The first[52] examined the efficacy of methylphenidate in 23 adults diagnosed with childhood-onset or current ADHD. Methylphenidate had a significantly higher response rate than placebo (78% vs. 4%, respectively, $p < .001$). In this study,[52] methylphenidate was begun at 0.51 ± 0.01 mg/kg/day and titrated to 1 mg/kg/day; response was shown to be more robust with increases in daily doses (Figure 3).

Another study[53] assessed the use of mixed amphetamine salts in adults with childhood-onset ADHD. A significantly higher percentage of patients treated with mixed amphetamine salts (70.4%, N = 27) improved with a reduction on the ADHD rating scale of ≥ 30% ($p = .001$) compared with placebo (7.4%, N = 27). Treatment with mixed amphetamine salts resulted in significant improvement in ADHD symptoms on the ADHD rating scale (42% decrease, $p < .001$) compared with placebo, with the reduction most often being seen in the first 3 weeks of treatment (Figure 4).[53]

Dr. Spencer and colleagues[54] also examined nonstimulant treatment. Figure 5[54] shows the pilot study results of 22 adult patients with childhood-onset ADHD treated with atomoxetine. After 3 weeks of atomoxetine treatment, the mean decrease in ADHD rating scale scores was significantly ($p < .001$) greater than the scores of patients who were treated with placebo. Of the 21 patients in the final analysis, 11 (52%)

responded to atomoxetine treatment compared with only 2 (10%) who responded to placebo.

In a 20-week, placebo-controlled study,[41] Weiss and colleagues examined the utility of combining psychotherapy with dextroamphetamine and/or paroxetine in adults with ADHD. ADHD symptoms improved with dextroamphetamine but not with paroxetine. Paroxetine was viewed by clinicians as improving mood and internalizing symptoms, although the HAM-A scores (which were low at baseline) did not show response. Study completers with ADHD and a lifetime SCID internalizing disorder had lower response rates to dextroamphetamine than those who had no internalizing disorder ($p = .042$). However, a moderating effect of an internalizing disorder was not evident in the intent-to-treat population.

In a 6-week randomized, placebo-controlled study of methylphenidate in adults with ADHD,[55] Spencer and colleagues found no differential effects on stimulant response between patients with ADHD only and those who also had comorbid anxiety. Of 146 patients, 56% (N = 82) had comorbid psychiatric disorders with 9% of those patients having multiple (at least 2 or more) anxiety disorders. One limitation of this study was the inclusion of only subjects who required no medication treatment for their comorbid disorders.

In a recent study of the nonstimulant atomoxetine, Spencer et al.[56] examined whether psychiatric comorbidity reliably predicted response to atomoxetine treatment in adults with ADHD. Findings showed that PTSD predicted atomoxetine-associated improvement on a number of clinical indicators including the Self-Rating Total subscale on the Conner's Adult ADHD Rating Scale and all 3 of the subscales on the General Well-Being Schedule. However, Dr. Spencer cautioned that this work was exploratory and needs replication.

Dr. Spencer warned that the HAM-A is widely used but detects mostly somatic anxiety symptoms and is less sensitive to other features of anxiety. Because many subjects do not score in the range indicating anxiety symptoms at baseline, the effects of treatment on anxiety are difficult to measure. Dr. Adler stated that although studies of stimulants and nonstimulants have examined anxiety symptom severity with rating scales such as the HAM-A and have found few effects of anxiety on response rates to ADHD treatment, the next generation of studies should incorporate feeling state questionnaires rather than the HAM-A, in order to address patients who are seriously impaired by anxiety symptoms but do not meet full diagnostic criteria.

Dr. Spencer said that he had been concerned that stimulant use in adults may have anxiogenic adverse effects. However, both stimulants and nonstimulants seem well-tolerated, and these studies did not describe exacerbation of any anxiety symptoms that were already present or development of anxiety in those who did not have anxiety at baseline. The same amount of caution should be observed when prescribing pharmacotherapy for adults with ADHD and comorbid anxiety as is used in children and adolescents.

Nonpharmacologic Treatment of ADHD and Comorbid Anxiety Disorders

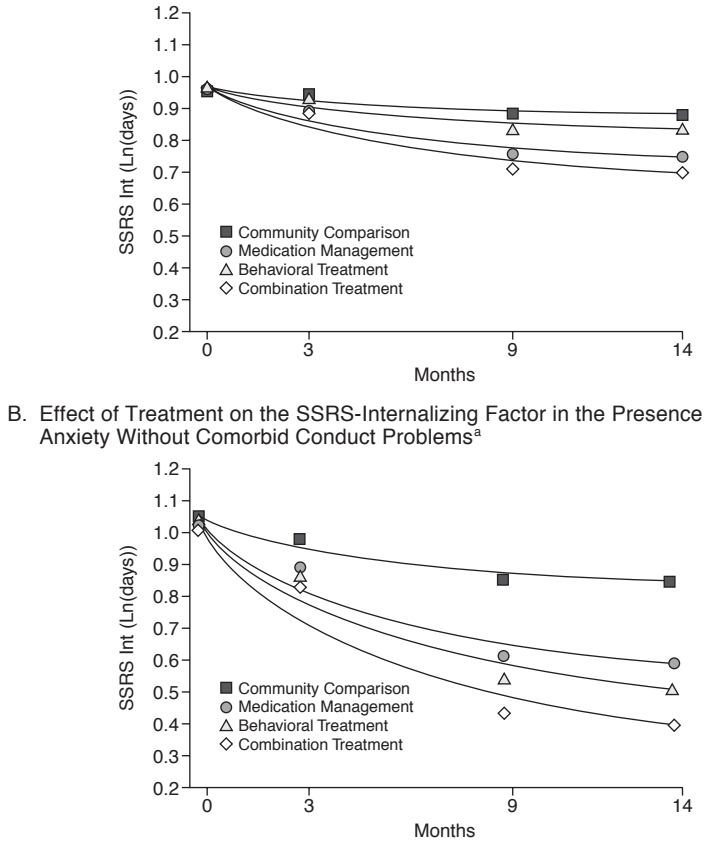
Dr. Adler suggested the group consider nonpharmacologic treatment options for patients with ADHD and comorbid anxiety. Most studies of psychotherapy in these patients implement pharmacotherapy as well, whether in children or adults. Dr. Adler stressed that CBT for ADHD should be differentiated from CBT for anxiety, because, as Dr. Spencer commented, the type of CBT used for ADHD may focus on organizational problems, rather than anxiety. Dr. Adler also noted that studies of CBT in patients with ADHD often focus on pure ADHD without comorbid anxiety.

Children

Dr. Barkley began the discussion of nonpharmacologic treatment of ADHD and comorbid anxiety by citing the MTA study,[57] in which 579 children with ADHD were randomly assigned to 14 months of treatment with either routine community care or 1 of the following treatments: intensive behavioral treatment, medication management (usually methylphenidate), or the combination. The anxious group of children with ADHD responded better to the combination treatment than to either treatment alone or to routine care. They also responded better to behavioral treatment alone than did the group with ADHD and no anxiety, and had a small but clinically significant differential improvement with combined treatment than medication alone (Figure 6).[58] According to Dr. Newcorn, in the MTA study,[57] two thirds of the children with ADHD and comorbid anxiety also had a comorbid behavioral disorder; the robust improvement to behavioral therapy alone was most evident in the group without conduct disorder. Other analyses from the MTA suggest that the group with ADHD and both anxiety and conduct disorder did best with combined medication and behavioral therapy.[59] One interesting aspect of the MTA results is that, although psychosocial treatment alleviated both ADHD symptoms and internalizing symptoms, the treatment was directed only at difficulties characteristic of ADHD and was not specific to anxiety or other internalizing symptoms. The findings suggested that at least some of the anxiety exhibited in children with ADHD is attributable to the core ADHD symptoms, and ameliorating these core symptoms can, in turn, improve anxiety or internalizing symptoms.

Dr. Barkley noted another study[60] that used social skills training as part of a psychosocial treatment package and found similar results: the children with ADHD who were anxious responded better to social skills training than did the children with ADHD who were not anxious. Dr. Barkley hypoth-

Figure 6. Average Trajectory of Treatment Effect for 4 MTA Treatment Groups[a]



[a]Reprinted with permission from March et al.[58]
Abbreviations: DISC = Diagnostic Interview Schedule for Children, MTA = Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder, SSRS = Social Skills Rating System.

esized that children with ADHD and comorbid anxiety may respond better to psychological or behavioral interventions than children with other subtypes of ADHD.

A recent study[61] examined the efficacy of adding intensive multimodal behavior therapy for 10 weeks to children with ADHD (N = 50) who were stable on methylphenidate treatment. Behavioral therapy was given to the child and parent, and teachers were given behavioral training as well. The study assessed child, parent, and teacher ratings of ADHD symptoms, anxiety, self-worth, social skills, and other domains. Substantial improvements were found on all outcome domains, whether children received behavior therapy plus medication or medication only, with no significant differences between treatments. The authors concluded that psychosocial treatment may not improve results for children who have been optimally titrated on methylphenidate treatment.

Adults

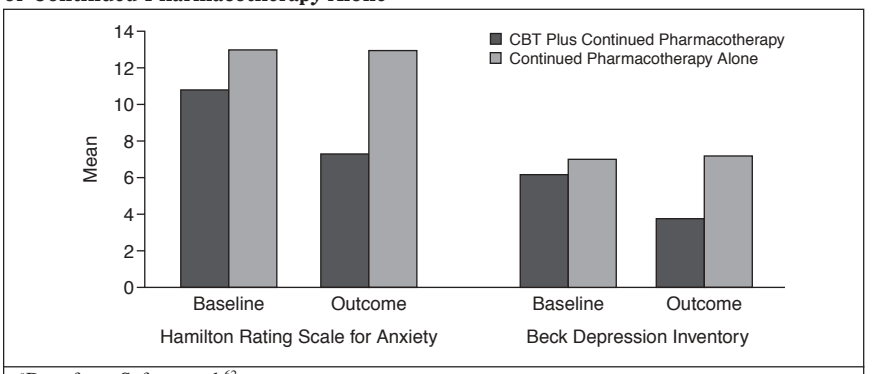
Dr. Spencer discussed a study by Safren et al.,[62] which examined the response to CBT in adults with ADHD. In this study, patients who had been stabilized on medication but still had clinically significant symptoms were randomly assigned to receive continued pharmacotherapy alone or pharmacotherapy plus CBT. The CBT was focused on organization, not anxiety; however, associated anxiety and depression were assessed in addition to ADHD severity. Despite the small sample size (N = 31), findings showed that adults who received CBT had significantly lower ratings of ADHD symptoms at endpoint than those who continued on pharmacotherapy alone (independent evaluator-rated symptoms, $p < .01$; Clinical Global Impression (CGI) score, $p < .002$; self-reported symptoms, $p < .0001$). The CBT group also had more treatment responders (56%) than the group that did not receive CBT (13%). The HAM-A and the Beck Anxiety Inventory both reflected significantly lower anxiety scores for patients receiving CBT ($p < .04$) (Figure 7).[62]

Dr. Spencer speculated that the human interaction involved in CBT might help patients with anxiety, even if the CBT is focused on organization rather than anxiety. However, he noted that a study using anxiety-targeted therapy, as opposed to therapy that focuses specifically on the ADHD symptoms, might be more illuminating. Dr. Newcorn stated that one advantage of psychosocial treatment is that it can be easily targeted to certain settings, times of the day, or certain kinds of behaviors. It is therefore possible to use psychosocial treatments for different conditions together and also in combination with medication.

Dr. Weiss discussed the Treatment for Adolescents with Depression Study (TADS)[63] in which patients were randomly assigned to 4 groups: fluoxetine alone, CBT alone, fluoxetine plus CBT, or placebo. Patients who were assigned to fluoxetine plus CBT treatment and fluoxetine-only treatment had higher response rates (71.0% and 60.6%, respectively) than those who were treated with CBT alone or placebo (43.2% and 34.8%, respectively). Due to the nature of psychosocial treatment, patients were not blinded to CBT treatment, which could have created expectancy effects. Dr. Weiss commented that patients are more likely to get better if they know that they will be assigned to an active treatment regimen than if they know that they will receive a placebo.

Dr. Weiss disclosed findings from a study[41] that examined the effects of pharmacotherapy and psychotherapy on adults who met DSM-IV criteria for ADHD (N = 98) but (for ethical reasons) excluded subjects who had a current anxiety or mood disorder of sufficient severity to require treatment in its own right. Patients had varying levels of internalizing symptoms, and most were subdiagnostic. Patients were randomly assigned to receive problem-focused therapy plus paroxetine alone, dextroamphetamine alone, both paroxetine and dextroamphetamine, or placebo for 20 weeks. Dr. Weiss believes that 2 findings from this study are important in terms of laying the foundations for replication in other research.

Figure 7. Mean Anxiety Score at Baseline and Outcome for Patients Randomly Assigned to Cognitive-Behavioral Therapy (CBT) Plus Continued Pharmacotherapy or Continued Pharmacotherapy Alone[a]



[a]Data from Safren et al.[62]

The first finding is that although scores on the HAM-A were low at baseline and showed no differential response to any treatments in the intent-to-treat sample, when using the CGI specific to anxiety and depression, clinicians gave a rating of much or very much improved to 100% of the paroxetine-only treated group (Figure 8).[41] This observation means that clinicians were noting improvement in areas in which the Hamilton rating scales and the CGI found little or no impairment to begin with. Clinicians seemed to be describing improvements in behaviors that the scales were not measuring, such as temper tantrums, a type of dysphoria, explosive reactions, and other symptoms not included as part of the DSM criteria.

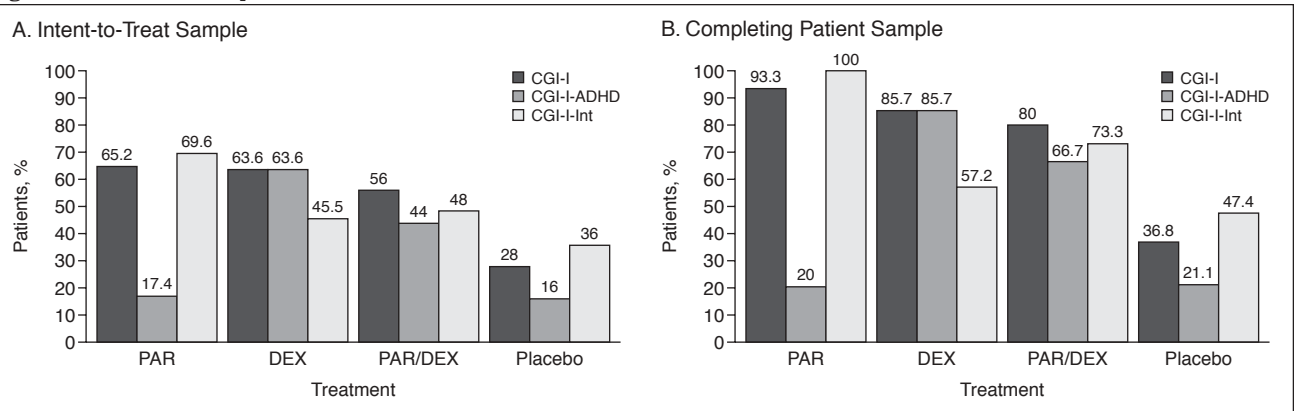
The second finding that deserves further exploration, according to Dr. Weiss, was that mood improved with paroxetine monotherapy and ADHD symptomatology improved with dextroamphetamine monotherapy, but the combination pharmacotherapy showed less improvement and more adverse events than either monotherapy in the domain they were used to treat.[41] Perhaps the greater number of adverse events caused lower doses to be used, thereby lowering the efficacy of the agents. Also, patients who received any medication plus psychotherapy responded better than those who received psychotherapy plus placebo, although the latter group did benefit substantially over time. Dr. Weiss stressed that more information is needed on the nature of the internalizing symptoms in adults with ADHD because although these symptoms do not fit into the DSM criteria or Hamilton rating scales for anxiety or mood disturbances, these symptoms may cause difficulties for patients who believe they need treatment and who are responsive to treatment. Others observed that there are no real guidelines for using medications together, and, as evident in this study, improved effectiveness across both disorders is not ensured. Results may vary as a function of dose and other considerations.

Psychosocial Treatment in Children Versus Adults

Dr. Adler asked how psychosocial treatments differ between children and adults. Having spoken with colleagues in the field, Dr. Adler believed that clinicians have different opinions as to whether psychosocial treatments should be used as primary therapies or augmentation strategies with medication. Dr. Newcorn suggested that psychosocial interventions are probably more often considered as potential primary treatments of childhood ADHD, whereas in adulthood they would often be used as part of an augmentation strategy. A major issue here is the nature of the psychosocial treatment used in different age groups. In children, the majority of research has been with parent behavior management approaches, directed at improving children's self-regulatory capacities. Cognitive behavioral approaches are likely to be better in older children or adults but target different domains of function.

Dr. Weiss pointed out that many children with ADHD have better self-esteem than one would expect for their difficulties, but that this protection may be eroded by anxiety disorders that increase insight and awareness of problems. However, Dr. Weiss continued that research on psychosocial treatments has started to convince her that there is a substantial difference between children and adults in respect to treatment, in that children have less insight, do not always see the need for treatment, and are often still symptomatic enough that they cannot use the lessons taught in psychosocial treatment. Cognitive behavioral therapy for ADHD may be much more useful for adults than for children. For example, children are still in school, where many psychosocial lessons are learned, whereas adults may benefit from the opportunity to learn skills such as having an agenda, keeping track of time, making appointments, and paying bills. Dr. Weiss stated that medication allows adults the capacity to do these tasks, but without skills training, they may have difficulty developing the new potential that arises from their decrease in symptoms.

Figure 8. Treatment Response in Adults With ADHD[a]



[a]Reprinted with permission from Weiss et al.[41]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-I = Clinical Global Impressions-Improvement scale, CGI-I-ADHD = CGI-I for ADHD symptoms, CGI-I-Int = CGI-I for mood and anxiety symptoms, DEX = dextroamphetamine, PAR = paroxetine, PAR/DEX = paroxetine and dextroamphetamine combined.

Table 4. A Summary of Findings on Issues of ADHD and Comorbid Anxiety in Children, Adolescents, and Adults

ADHD is a common disorder in children, adolescents, and adults that is often comorbid with other psychiatric disorders such as anxiety disorders
Children and adolescents with ADHD experience academic and social impairment as a result of their illness; impairment continues through adulthood and may be worsened by anxiety symptoms
Patients should be directly questioned about anxiety and ADHD symptoms, even if they are children
Although treatment guidelines are readily available, a high degree of variability in treatment practice exists in the clinical setting
Pharmacotherapy is the standard of treatment for ADHD; evidence is inconclusive about the use of psychotherapy in patients with ADHD and anxiety

Conclusion

The experts concluded that ADHD is often comorbid with anxiety disorders or encompasses symptoms of anxiety (Table 4). ADHD leads to significant impairment in children, which can continue into adolescence and adulthood. Anxiety disorders in particular are present in children with ADHD, but likely increase with age. The experts recommended interviewing patients specifically about the symptoms of ADHD and anxiety, even if the patient is a child. Comorbid anxiety may impact the course of illness as well as the types of treatments selected. Pharmacotherapy is effective, but more research on psychosocial treatments in this population is needed. Data are mounting regarding the importance of identifying comorbid anxiety disorders when treating individuals with ADHD, and this remains quite an active area of research.

Drug names: atomoxetine (Strattera), buspirone (BuSpar and others), dextroamphetamine (Dexedrine, Dextrostat, and others), fluoxetine (Prozac and others), methylphenidate (Metadate, Ritalin, and others), paroxetine (Paxil, Pexeva, and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, atomoxetine, dextroamphetamine, and methylphenidate are not approved by the U.S. Food and Drug Administration for the treatment of anxiety symptoms; buspirone is not approved for the concomitant treatment of attention-deficit/hyperactivity disorder (ADHD); and fluoxetine and paroxetine are not approved for the treatment of ADHD symptoms.

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For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 491–493.

