A CE Monograph Based on the APSARD Annual Conference held November 5 – 6, 2010

ADHD Current Concepts and Future Developments

PROGRAM OVERVIEW

Ongoing clinical and scientific advances have transformed the field of attention-deficit/hyperactivity disorder (ADHD). Substantial knowledge has been gained on the neuropathology; neurobiology; heritability; environmental, persistence, comorbidity, psychotherapeutic and pharmacological treatment of ADHD in children, adolescents, and adults. This continuing education (CE)-accredited course will feature nationally renowned ADHD faculty who will present recent research findings relevant to clinical practice, with a focus on adolescent and adult patients.

TARGET AUDIENCE

This activity is designed for child and adult psychiatrists, psychologists, primary care physicians, pediatricians, nurse practitioners, and other allied mental health and medical experts working to improve the quality of care for adolescent and adult patients with ADHD across the clinical continuum.

LEARNING OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Increase clinical inquiries and screening for ADHD in adolescent and adult patients to improve detection rates
- Apply criteria to definitively diagnose ADHD and identify potential comorbid conditions such as mood disorders and substance use disorders in adolescents and adults
- Understand the role of pharmacotherapy and nonpharmacotherapy modalities of treatment in the management of adolescent and adult ADHD patients
- Develop a strategy for tailoring individualized, comprehensive treatment plans and monitoring for medication adherence to effectively treat and manage ADHD in adolescent and adult patients
- Review potential cardiovascular risks associated with some ADHD treatments and understand how to conduct a thorough clinical review to screen for at-risk patients
- Understand the value of neuropsychological tests and rating scales along with performing a thorough clinical interview utilizing *DSM-IV* criteria
- Summarize the benefits of cognitive-behavioral therapies to improve outcomes for ADHD patients

GENERAL INFORMATION

Release Date: June 6, 2011
Expiration Date: June 6, 2012
Estimated Time to Complete This Activity as Designed: 60 minutes

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ADHD
Current Concepts
and **Future Developments**

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ADHD Current Concepts and Future Developments

Abstract

Attention-deficit hyperactivity disorder (ADHD) is a common, chronic condition of childhood that often persists into adulthood. The disorder is associated with a variety of educational, workplace, social, and functional impairments throughout the patient's life span. Recent advances in the assessment and management of ADHD in adults were discussed by a group of experts at the 2010 Annual Conference of the American Professional Society of ADHD and Related Disorders (APSARD). These presentations explored current issues related to functional impairment, comorbidity, pathophysiology, assessment, and treatment. Deficits in executive functioning (EF) are particularly important for adults with ADHD, although EF is a multidimensional construct and not easily assessed with available tests. Management options for ADHD symptoms and functional impairments include both pharmacotherapy (stimulants and nonstimulants) and nonpharmacologic therapy. In addition, any treatment regimen must consider comorbidities, safety concerns, and the potential for drug misuse or diversion. These presentations underscore the complexity of ADHD management and the need for clinicians to have a thorough understanding of issues related to pathophysiology, assessment, and treatment to ensure that patients receive optimal therapy for ADHD and concomitant disorders.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattentiveness, impulsivity, and hyperactivity, and it is one of the most common childhood psychiatric conditions. The cumulative prevalence of ADHD is 6% to 8%, and the disorder persists into adolescence and adulthood in the majority (ie, 60% to 85%) of patients.[1] ADHD is associated with numerous functional deficits, including impairments in academic and work performance as well as psychological, social, and familial dysfunction.

Over the last few years, there has been substantial progress in the assessment and management of ADHD. These developments were reviewed by a group of experts at the 2010 Annual Conference of the American Professional Society of ADHD and Related Disorders (APSARD). These presentations explored a number of current issues related to functional impairment (eg, deficits in executive functioning [EF]), comorbidities, pathophysiology, assessment, and treatment in patients with ADHD. This monograph reviews the highlights of these discussions.

Executive Functioning (EF) and Adaptive Impairment in ADHD: Current Findings and a New Theory of EF

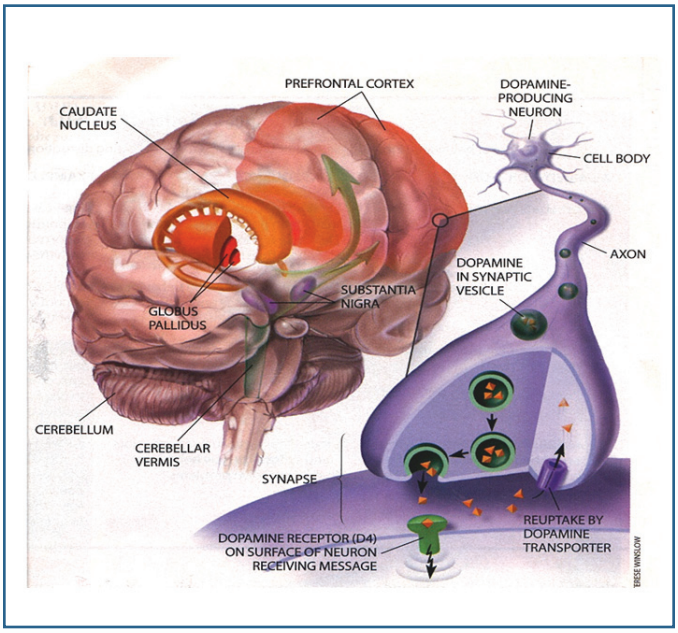

Figure 1. ADHD is associated with reduced brain volume and activity in 5 regions that contribute to EF.[3]

ADHD is considered to be, at least in part, related to an impairment in EF.[2] Although there is no single agreed-upon definition of EF, it involves mental processes used in problem solving that include task analysis, strategizing, executing, and regulating goal-specific tasks. The neural networks involved in EF deficits are illustrated in **Figure 1**.[3] In particular, differences in prefrontal projections appear to be a critical element of the pathogenesis of ADHD. This includes the frontal-striatal circuit (associated with deficits in response suppression, freedom from distraction, working memory, organization, and planning), the frontal-cerebellar circuit (associated with deficits in motor coordination and behavioral timing), and the frontal-limbic circuit (associated with symptoms of emotional dyscontrol, motivation deficits, hyperactivity-impulsivity, and proneness to aggression).

Although there is no single agreed-upon definition of EF, it involves mental processes used in problem solving that include task analysis, strategizing, executing, and regulating goal-specific tasks

Despite the linkage of ADHD to EF deficits, data indicate that only 35% to 50% of cases of ADHD fall in the impaired range of EF tests.[4] However, the correlation between EF tests and ratings of EF in daily life is poor. Most EF tests were not

developed to assess EF and do not represent the construct well. Thus, EF tests are not assessing the same construct(s) as EF rating scales and have low predictive value for daily adaptive functioning.

A study of 158 children diagnosed with ADHD between 1978 and 1980 (Milwaukee Study) was conducted to determine the level of EF deficits associated with ADHD and to evaluate the relative merits of EF tests compared with EF rating scales in predicting impairment in various domains of adaptive functioning.[4] The results indicated that EF tests contributed just 2% to 8% of the variance in EF ratings and that EF tests are largely unrelated to EF rating scales. Overall, EF rating scales were found to be much more highly related to ADHD symptoms than were EF tests. EF scales predicted up to 45% of variance in global self-rated impairment and 20% in other rated impairment, whereas EF tests predicted ≤6% in global self-rated impairment and 7% in other ratings. These results are consistent with other studies comparing different EF tests with ratings of EF and adaptive functions.[4]

To understand these discrepancies, it is important to understand that EF is not a unitary construct but a multilevel meta-construct having an extended phenotype. A 6-level model having 4 hierarchically organized levels or concentric rings of phenotypic effects of EF better fits the evidence and conceptualization of EF (**Figure 2**). These include the pre-executive, instrumental/self-directed, adaptive/self-reliant, tactical/interactive, strategic/cooperative, and utilitarian/outcomes levels. The first 5 levels are related to EF, whereas the sixth level (utilitarian/outcomes) reflects the long-term outcomes of EF for a person's longer-term welfare. Although ADHD disrupts all 5 levels of EF, the tactical and strategic levels are particularly affected, thereby creating a disorder of self-regulation across time. ADHD also can be considered as "time blindness" or "temporal neglect syndrome." It adversely affects the capacity to hierarchically organize behavior across time to anticipate the future and to pursue one's long-term goals and self-interests. Thus, ADHD is not an attention deficit but an intention deficit (ie, inattention to mental events and the future). It is a disorder of performance, not skill.

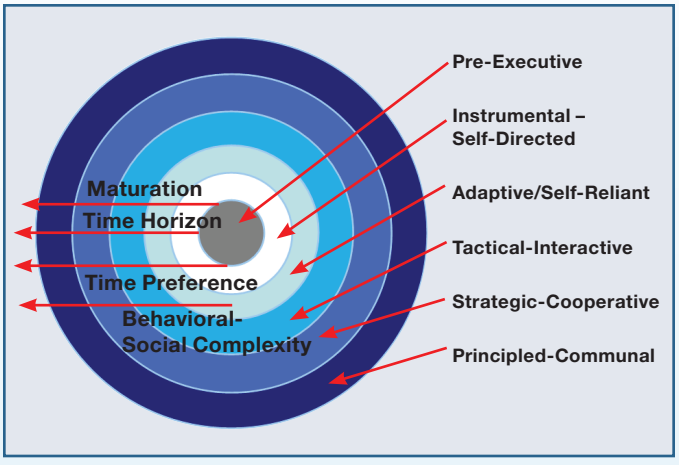

Figure 2. Six-level extended phenotype of EF.

This construct has implications for treatment. The key is to design prosthetic environments around the individual to compensate for his or her EF deficits. Therefore, effective treatments are always those at the "point of performance." Because EF deficits are neurogenetic in origin, medications may be essential for most cases, although behavioral treatment is essential for restructuring natural settings to assist the deficient EFs.

EF is not a unitary construct but a multilevel meta-construct having an extended phenotype

The Road to Practice Principles

APSARD is a relatively young organization and, as such, has yet to develop practice guidelines for the management of ADHD. For a society to develop practice guidelines, which establish definitive practice parameters, they must follow strict guidelines. In contrast, practice principles are overarching concepts that may not be as difficult to develop. Thus, APSARD is currently in the process of developing practice principles regarding the assessment and treatment of ADHD.

Areas of consideration for assessment include:

- Use of scales (diagnostic and symptom assessment)
- Use of symptom scales to monitor treatment
- Obtaining comprehensive history
- Obtaining records and additional informant(s), if feasible

Areas of consideration for treatment include:

- Role of medication and psychosocial treatments
- Treating adequately and addressing target symptoms
- Monitoring response and following patients regularly
- Individualizing treatment plan
- If medication is used, monitoring blood pressure/pulse
- Differentiating "better" from "well"
- Establishing some guideline for how long to treat and how to taper medication, while carefully monitoring for potential relapse
- Preferential use of a long-acting agent

Pharmacogenetics in ADHD: An Update

There is substantial variability in treatment response (ie, efficacy, safety) among patients with ADHD. This may be partly explained by the unique pharmacological profiles of ADHD drugs, but genetic mechanisms may also contribute to individual variations in outcomes. Molecular genetic studies have demonstrated that genetic variation exists at relevant targets, strongly suggesting a genetic basis for response.[5,6] Independent genome-wide scans implicate region 17p and possibly 5p.[7] For example, genes that code for the dopamine receptor (DRD4) have been associated with ADHD.[5,8] Altered expression of the synaptosomal-associated protein of 25 kDa (SNAP-25) has also been implicated in the phenotypic expression of ADHD.[9] However, although genetic scan results suggest a clear genetic component to ADHD, the contribution of individual candidate genes to ADHD appears to be small.

Preliminary data suggest a likely genomic role in drug response and the development of adverse events

Early data suggest a likely genomic role in drug response and the development of adverse events, but better studies are needed.[10] For example, polymorphisms in the dopamine transporter gene (DAT1), the adrenergic α2A receptor gene (ADRA2A), and the 5HT transporter gene have been associated with response to methylphenidate (MPH).[11-13] Polymorphic variations (eg, DRD4 and cytochrome P450 2D6) have also been implicated in the risk of developing adverse events to ADHD therapy.[12,14]

Although genetics certainly plays a role in the pathogenesis of ADHD and in response to therapy, it is unknown whether these genetic effects are due to multiple genes with a small effect or to rarer genes that confer moderate risk. Further studies should shed light on the heterogeneity of symptom severity and the course and variation in treatment response. Because the cost of genotyping is decreasing rapidly, genetic information will be more readily accessible, further promoting efforts to apply individual genetics to treatment prediction and matching.

Cognitive Training Technologies

Working memory training and neurofeedback have been subjected to more rigorous study in recent years and have produced some positive results in the treatment of ADHD. However, there remain important questions regarding their effectiveness and the generalizability of gains. These methodologies are best considered to be complements rather than alternatives to medications, although these approaches may be attractive to patients with insufficient response or in those who desire to avoid "traditional" medicine. ADHD is associated with working memory deficits that contribute to other impairments in executive functions and problem solving. There are various interactive, computerized programs that are generally based on the "exercise" principle of improving brain functioning in which the patient undergoes a "mental boot camp." These cognitive training programs are designed to increase cognitive skills (eg, working memory, auditory and visual processing, and reading skills). The training is typically done at home on a personal computer and supported by a trained coach. In healthy adults, working memory training has been shown to increase brain activity that is related to working memory (ie, middle frontal gyrus, superior and inferior parietal cortices).

There have been a few small studies evaluating working memory training in ADHD, primarily performed in children and teens.[15,16] In a randomized, multicenter study involving 53 children aged 7 to 12 years with ADHD, working memory training was associated with improved performance in working memory tasks and complex reasoning, with most benefits persisting after 3 months of follow-up.

The improvements in working memory induced by such training have also been shown to be associated with changes in cortical dopamine D1 receptor binding in healthy adult males who completed the training, underscoring the biochemical basis of mental activity.[17] However, many of these studies have been conducted by the developers of the training program. Independent studies of the effectiveness of working memory training, including that provided to adults with ADHD, are still needed.

Working memory training has been shown to increase brain activity in brain areas that are related to working memory

Neurofeedback involves the placement of sensors on the scalp to measure the electrical activity of the brain. Neurofeedback training involves targeting brain-wave frequency profiles associated with ADHD. Up-training (reward frequencies) involves frequencies associated with better attention and down-training (inhibitory frequencies) involves frequencies associated with distractibility through the use of rewards on some interactive program, such as being able to earn points on a video game when the targeted frequencies stay within the appropriate range. This therapeutic modality may have a role in the treatment of ADHD because ADHD is associated with high theta waves (4–8 Hz) that are involved with creativity, insight, deep states, drowsiness, and low beta waves (13–21 Hz) that are associated with sustained focused attention. Recent published, randomized, controlled trials in children with ADHD suggest that neurofeedback therapy may be an effective modality. For example, in a study of 102

children aged 8 to 12 years with ADHD, neurofeedback training was superior to a control group on both teacher and parent rating scales.[18]

Although promising, these results require independent replication. Some aspects of the design might have influenced the results, such as simultaneously training 2 children at a time. Nevertheless, research is ongoing, study designs are improving, and the pending results of ongoing studies should help to clarify the role of this complementary treatment modality.

Assessing Functional Outcomes in Young Adults with ADHD

Adult ADHD is associated with significant impairments in multiple domains (eg, educational, social, functional)[19,20]; however, the disorder is underdiagnosed.[19] One of the primary obstacles to the diagnosis and treatment of adults with ADHD is that most physicians were not trained to consider ADHD in the differential diagnosis. This is important because missed diagnoses of ADHD are a common contributor to treatment failure for other psychiatric conditions. The diagnosis of adult ADHD is also complicated by the fact that diagnostic criteria (ie, *DSM-IV*) contain childhood-specific items not appropriate for adults. Furthermore, inattentive symptoms predominate in adults, and hyperactivity symptoms typically decrease by adulthood (**Figure 3**).[21]

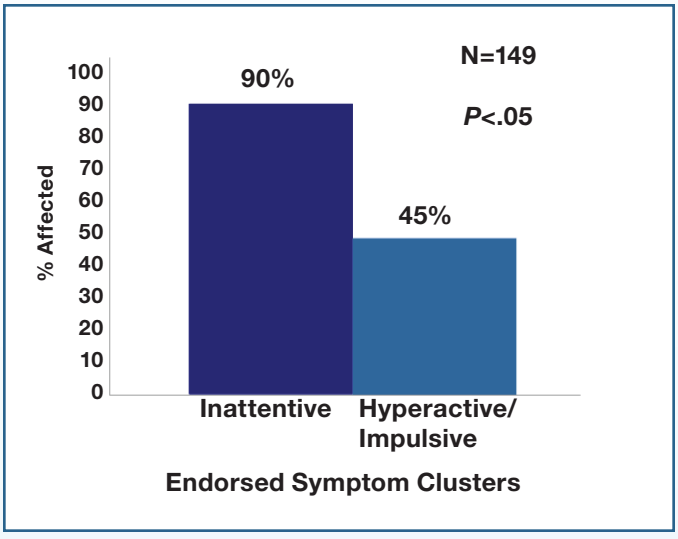

Figure 3. Inattention versus hyperactivity/impulsivity in adults with ADHD.[21]

The evaluation of adult ADHD can be complex because the core symptoms of the disorder are not present in all individuals and because comorbidity is common.[22] In addition, the requirement for impairment in 2 realms of life can be difficult to determine, especially for high-functioning patients. Thus, primary care physicians (PCPs) often lack confidence regarding diagnosis. For example, in a recent survey of PCPs, only 34% felt that they were either very or extremely knowledgeable about adult ADHD (**Figure 4**).[23]

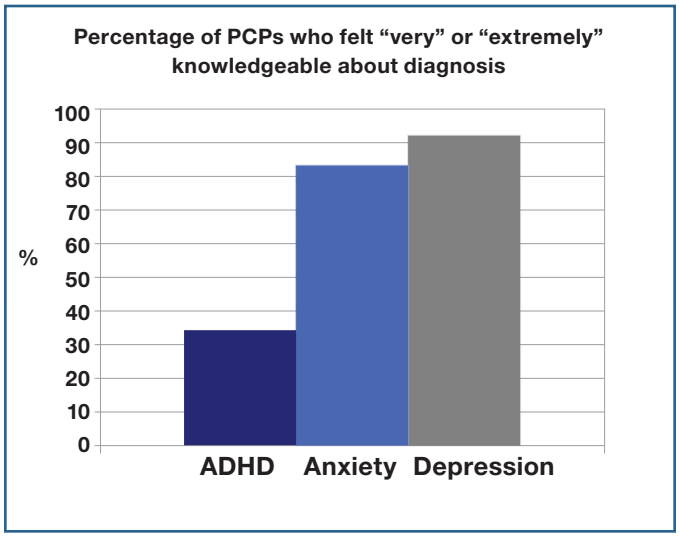

Figure 4. Confidence of PCPs with the diagnosis of ADHD and other psychiatric disorders.[23]

Several rating scales are available for the diagnosis of adult ADHD or for symptom assessment. Diagnostic instruments include the Conners' Adult ADHD Diagnostic Interview, Barkley Current Symptoms Scale, Brown ADD Scale Diagnostic Form, Kiddie-SADS Diagnostic Interview ADHD Module, and the Adult ADHD Clinician Diagnostic Scale (ACDS) v1.2. Neuropsychological testing can also be performed to assess impairments in EF in adult ADHD, although these tests are generally for educational rather than diagnostic purposes. The 6 most consistently used and employed neuropsychological tests are Continuous Performance Test, Stroop Color-Word Test, Trail Making Test, Verbal Fluency Test, Controlled Word Association Test, and the Weschler Adult Intelligence Test.[24] These tests are useful for providing corroborative information but are insufficient for establishing a diagnosis. The goal is to anchor neuropsychological test results with clinical symptoms.[24]

The evaluation of adult ADHD can be complex because all of the core symptoms of the disorder are not present in all individuals and because comorbidity is common

Management of EF deficits in young adults with ADHD includes psychosocial/cognitive-behavioral therapy (CBT) and medication (stimulants and nonstimulants).[25] In 88 adults with ADHD, meta-cognitive therapy (a form of CBT) was associated with self-reported and independent

evaluator ratings of inattentive symptoms compared with supportive therapy.[26] Biederman and colleagues[27] evaluated the effects of stimulants on neuropsychological tests in a group of transitional adults. The study included 3 cohorts: ADHD patients on stimulants, ADHD patients who had not received stimulants for ≥1 month, and non-ADHD controls. ADHD patients receiving stimulants had higher neuropsychological measures of attention (but not other measures of EF) compared with subjects with ADHD who did not take stimulant medication. Atomoxetine has also been shown to be effective for improving EF in one study of adults with ADHD.[28] This included improvements in all clinical measures of EF, including activation, focus, effort, emotion, and memory.

ADHD and Family Issues

One of the most important impairments of ADHD is the disorder-related influence on family life. There are at least 2 aspects of this effect: 1) the influence of having a child with ADHD on family life, and 2) the influence of being an adult parent with ADHD on family life. Furthermore, because ADHD is heritable, both of these conditions can coexist in the same family. The presence of ADHD in children is associated with disrupted parent-child relationships, role dissatisfaction, feelings of incompetence and insecurity of the parents, a high degree of stress, and financial burden.

Parenting style and attitude can have an impact on family dynamics. Parents who express greater awareness of disorder appear to have a greater tolerance of behavior; however, denial of the problem is very common.[29] Parents' attitudes toward their ADHD child influences their attitude toward treatment in general and medications in particular. Most parents are highly ambivalent about medicating children, and many parents prefer to employ self-care strategies (eg, behavior modification, coping, diet, religious practices) alongside professional therapy as an alternative to pharmacotherapy.

Diagnosing and treating family members (ie, parents and siblings) as well as the child with ADHD is crucial in optimizing parent-child interactions and parental psychiatric status, as well as improving the long-term outcomes for the child and family

Diagnosing and treating other family members (ie, parents and siblings) as well as the identified child with ADHD is crucial in optimizing parent-child interactions and parental psychiatric status, as well as improving the long-term outcomes for the child and family.[30] Family treatments (eg, parenting programs) are an important component of the integrative treatment.[31] These include behavior training, parental education, and family therapy, with the specific type of therapy optimally being tailored to the individual family.

ADHD and Eating Disorders

Eating disorders are typically thought of as primarily a condition of adolescent or young adult females, whereas ADHD is typically thought of as a condition of prepubertal boys, with a peak age of diagnosis of 6 to 8 years. Eating disorders have a 6- to 10-fold higher prevalence in females, whereas ADHD has a 3-fold higher prevalence in males.[1,32] However, although these general perceptions are true, this also means that girls and adolescents/adults are underrepresented in the ADHD literature.

ADHD and eating disorders are inter-related, and there is a plausible theoretical relationship between the two

ADHD and eating disorders are inter-related, and there is a plausible theoretical relationship between the 2 disorders. For example, girls with ADHD may show distress through eating disorders. Alternatively, ADHD-related impulsivity may be considered as a disorder of "behavioral inhibition" and manifest as an eating disorder.[33]

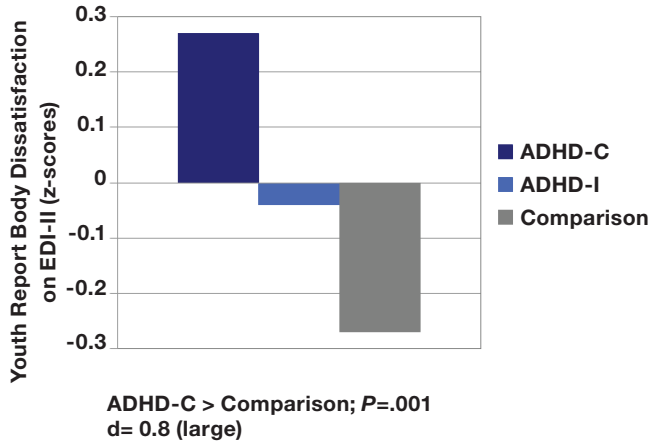

Figure 5. Youth report of body dissatisfaction.[33]

A prospective study of eating disorders in 228 girls with ADHD found that girls with ADHD-Combined type (ADHD-C) had a greater association with eating pathology at follow-up than those with ADHD-Inattentive type

(ADHD-I) and a comparison group. In this study, girls with ADHD-C also had greater body dissatisfaction (**Figure 5**) and more frequently reported bingeing and purging.[33] Although the girls with ADHD-C and ADHD-I both had higher body mass index (BMI) than the comparison group, controlling for this did not change the finding that girls with childhood ADHD-C had more bingeing and purging by adolescence. The study also found that childhood impulsivity was the best predictor of bulimia nervosa (BN) symptoms, even after controlling for childhood inattention and hyperactivity. Childhood peer rejection and childhood critical/intrusive parenting also predicted adolescent BN symptoms, and these problems were more common in those with ADHD-C. Furthermore, a concurrent diagnosis of ADHD-C was not as predictive of BN as was ADHD-C in childhood. The authors hypothesized that this was likely because many girls with ADHD-C in childhood had a change in diagnosis (ie, to ADHD-I, ADHD-NOS, or no diagnosis) by the time that they had reached adolescence.[33]

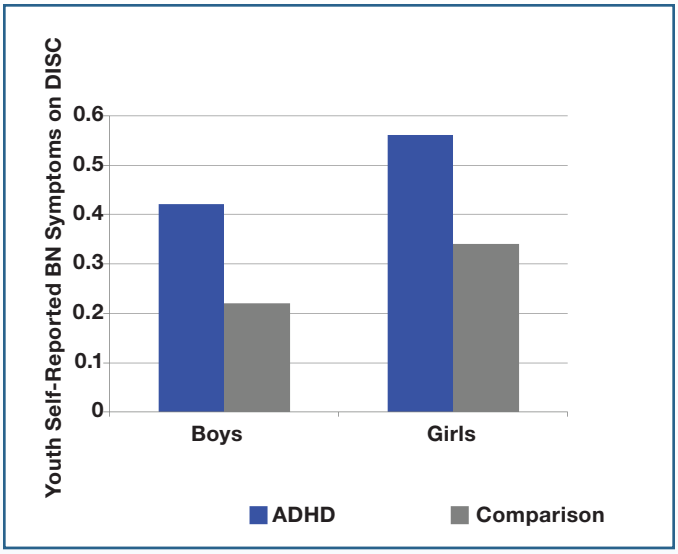

Figure 6. Youth report of BN symptoms.[34]

A follow-up study of the subjects in the Multimodal Treatment Study of ADHD (MTA)[34] investigated the body image dissatisfaction and bingeing/purging characteristics in 337 boys and 95 girls with ADHD 8 years after their MTA recruitment (current ages 15–17) and in a grade- and sex-matched comparison group.[35] Overall, the results indicated that girls and boys with ADHD-C displayed more BN symptoms than their respective comparison groups (**Figure 6**).[35] Both the adolescent girls and boys with ADHD had higher mean BMIs than their respective comparison groups, but controlling for differences in BMI did not alter the results demonstrating more BN symptoms in the childhood ADHD subjects. Childhood impulsivity predicted adolescent BN symptoms even after controlling for inattention and hyperactivity. Overall, these findings indicate that the risk for BN may persist even when ADHD symptoms do not and that childhood impulsivity may be expressed as disordered eating in adolescence.

Eating disorders should be assessed in children with ADHD. Clinicians should ask adolescents/parents about eating disorders and adolescents should be given self-report questionnaires (eg, Eating Attitudes Test [EAT], Eating Disorder Inventory II [EDI-II]). Clinicians should also watch for signs of potential BN pathology (eg, high/changing BMI, digestive, esophageal, or dental problems). Longer-term treatment of ADHD may prevent BN,[35] but studies regarding the efficacy of such interventions for amelioration of BN symptoms are inconclusive. Separate BN treatments (eg, CBT, pharmacotherapy) may be required.

Clinicians should ask adolescents/parents about eating disorders and should watch for signs or potential BN pathology

Treatment of Co-occurring ADHD and Substance Use Disorders: Implications of New Findings for Clinical Practice

Comorbidity of adult ADHD and substance use disorder (SUD) is common. Data from the National Comorbidity Survey Replication study found that 10.8% of respondents with SUD had concomitant ADHD compared with an ADHD prevalence of only 3.8% among adults with no comorbidities. Among adults with ADHD, 15.5% had concomitant SUD, compared with a SUD prevalence of only 5.6%, among those with no comorbidities.[36] Individuals with ADHD presenting for treatment very commonly have SUD. In one study, 40% of ADHD patients presenting for treatment had a history of SUD and another 10% were currently substance abusers.[37] The overlap may be related to self-medication or ADHD-related impulsive behaviors. At the biochemical level, there is possible involvement of the dopamine reward pathway.[38] Adult ADHD was recently found to be associated with decreased D2/D3 receptors and dopamine transport in limbic brain areas, suggesting that abnormalities in this dopamine reward pathway increase vulnerability to substance abuse.[38]

Data from the National Comorbidity Survey Replication study found that 10.8% of respondents with SUD had concomitant ADHD and 15.5% of those with ADHD had concomitant SUD

There has been concern that ADHD pharmacotherapy is a risk factor for subsequent substance abuse. However, data from a meta-analysis suggest that stimulant

treatment of ADHD does not increase the risk of SUD.[39,40] There is even evidence that prior pharmacotherapy may be protective against subsequent SUD (**Figure 7**).[41] In a laboratory study, the combination of oral, sustained-release methylphenidate (MPH-SR) twice a day, and intravenous cocaine did not produce synergistic effects. In fact, there was an indication that oral MPH-SR may even reduce the likelihood of self-administration of cocaine.[42]

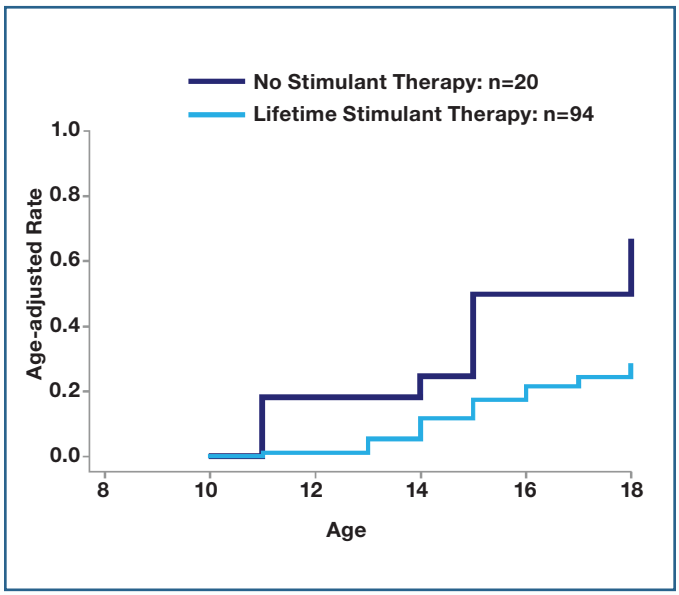

Figure 7. Impact of prior stimulant treatment for ADHD for risk of subsequent SUD in adolescent girls.[41]

Studies assessing the treatment of SUD in individuals with ADHD have produced mixed results. In the largest study to date (CTN trial),[43] 300 adolescent substance abusers received osmotic-release MPH (OROS-MPH) or placebo. There was no significant difference between treatment groups for the primary ADHD or substance use outcome measures, although there was greater improvement in ADHD symptoms and substance use on secondary outcome measures.

Atomoxetine may be particularly effective for abstinent alcohol-dependent individuals. In a study of 147 adults with ADHD and SUD, atomoxetine-treated patients achieved significantly greater improvements in ADHD symptoms compared with those receiving placebo (**Figure 8**).[44] There was no significant difference between groups for the time-to-relapse of heavy drinking; however, cumulative heavy drinking days were reduced 26% in the atomoxetine group.[44] An ongoing multisite trial is evaluating 2 doses of extended-release mixed amphetamine salts versus placebo for cocaine-dependent adults with ADHD. In addition, there are recent data suggesting that behavioral therapy plus medication may be superior to medication alone for substance abusers who have partial responses.[45]

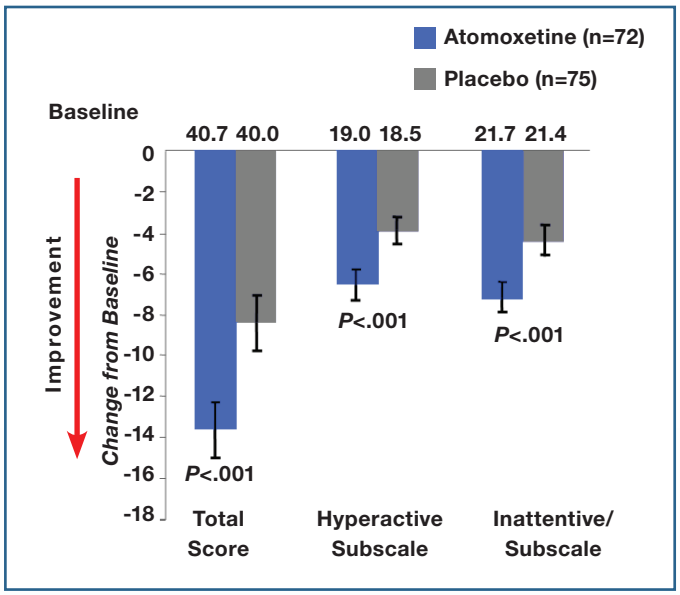

Figure 8. Efficacy of atomoxetine for the treatment of ADHD in adults with recently abstinent alcohol use disorders.[44]

Overall, stimulant use in patients with an active SUD is complex and remains controversial. If the decision is made to use stimulants, extended-release formulations are preferred and both ADHD symptoms and the pattern of alcohol/drug use should be monitored closely. In addition, the clinician should watch for red flags that might suggest diversion or misuse. If severe SUD is present, the patient should be referred for intensive intervention prior to starting medication for ADHD.

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Recognition and Assessment of Adult ADHD in Primary Care

ADHD is common in adults. It is estimated that ADHD may affect >9 million adults (4.4%) in the United States, and there may be as many as 8 million adults with ADHD who do not receive pharmacologic treatment.[36] Although ADHD is among the most prevalent psychiatric disorders in adults, PCPs are not comfortable with diagnosing ADHD. However, diagnosing adult ADHD is important because it significantly impairs function and is associated with multiple psychiatric and medical comorbidities.

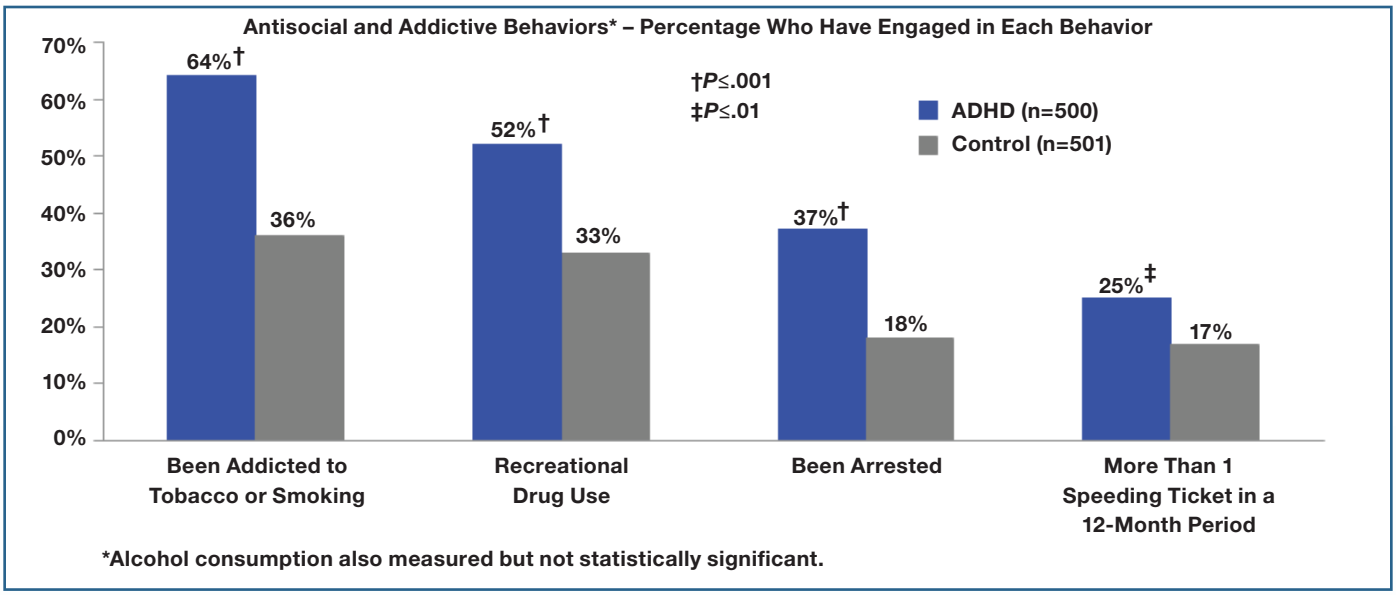

Figure 9. Effect of ADHD on antisocial and addictive behaviors in adults with ADHD.[19,46]

Compared with non-ADHD controls, adults with ADHD have lower educational achievement, socioeconomic status, and income level, along with higher rates of unemployment, relationship problems, impaired driving, and comorbid mental illness (eg, depression, anxiety, substance abuse, and cigarette smoking) (**Figure 9**).[19,46] For example, adults with ADHD change jobs more often than non-ADHD controls; in one study, 43% of adults with ADHD reported leaving at least 1 job in the last 10 years due, at least partly, to ADHD symptoms.[19]

Diagnosing adult ADHD is important because it significantly impairs function and is associated with multiple psychiatric and medical comorbidities

Most primary care practitioners may see at least 1 patient with undiagnosed ADHD each day. However, the recognition and diagnosis of adult ADHD is challenging. Many adults with ADHD (approximately one-half) are self-referred, presenting after they, family members, or friends suspect that they might have the disorder.

Some cardinal symptoms include: poor concentration; general disorganization; difficulties at work; or symptoms of inattention, impulsivity, or anxiety.[47] Many ADHD patients present with a comorbid disorder as their chief complaint (eg, depression, anxiety, SUD), and this may mask the symptoms of ADHD initially. Thus, the symptoms of ADHD may overlap with, or may be mistaken for, another psychiatric disorder, confounding the proper diagnosis and treatment of ADHD.

The proper diagnosis of adult ADHD is based on a careful clinical assessment, including symptoms, degree of impairment, family history, rating scale scores, and when possible, an interview with a spouse or family member. The diagnosis should not rely primarily on neuropsychological testing or screening tools. One clinical challenge in diagnosing adults with ADHD is that the *DSM-IV* criteria were developed for the diagnosis of ADHD in children. Therefore, there is a need to translate those diagnostic criteria into corresponding symptoms that would be expected in adults with ADHD (eg, poor time management, poor concentration, disorganization, procrastination, workaholism, constant activity, driving too fast, smoking/excessive caffeine). Screening tools such as the Adult ADHD Self-Report Scale (ASRS-v1.1) *(Available at: www.hcp.med.harvard.edu/ncs/ftpdir/adhd/18%20Question%20ADHD-ASRS-v1-1.pdf)*, coupled with the ADHD-RS v. 1.1 (with both adolescent and adult prompts), can be valuable. Although symptom assessment is important, early onset, chronicity, pervasiveness, and life impairment are crucial to the diagnosis. Clinicians should be cautious about attributing ADHD symptoms to comorbid disorders such as anxiety and depression, and should not use drug response as a means of diagnosing ADHD. Pharmacotherapy can be effective; it should be remembered that only long-acting agents are approved for the treatment of adults with ADHD.

Test and Workplace Accommodations and the Americans With Disabilities Act Amendments Act (ADAAA)

Because ADHD is associated with a wide range of impairments, patients with the disorder may be eligible for coverage under the Americans with Disabilities Act Amendments Act (ADAAA). The intent of the ADAAA is to prevent discrimination, not to help people succeed or guarantee success (ie, it is outcome neutral).

Qualifying an individual as disabled requires current, detailed, and professional documentation.[48] The documentation needs to establish current impairment, and the assessment should be conducted by a qualified professional and supported by comprehensive documentation, including first-hand historical records when possible. In particular, there should be credible documentation that establishes a chronic and pervasive pattern of impairment over time and across situations. It is important to understand that symptom severity or the number of symptoms endorsed on an ADHD rating scale do not necessarily translate into real-world functional impairment. Examples of persuasive documentation include early evaluation reports from childhood (eg, clinical evaluations, report cards, teacher comments, Individualized Education Plans, 504 Plans), descriptions of why parents sought help during childhood, evidence of attempts to gain control of symptoms/behavior, job performance reviews, and credible documentation from collateral informants (eg, parents, tutors, academic support personnel, teachers, professors, supervisors, coaches, etc).

Requested accommodations should address specifically the interactions between functional impairments and task domains, and should flow logically from the history of functional impairment

The requested accommodations should only address specifically the interactions between functional impairments and task domains, and should flow logically from the history of functional impairment.

Accommodations are not granted merely on the basis of a diagnostic label, and a case must be built from the history and evaluation data, demonstrating logically why the person needs the particular accommodation requested. There should be a cogent rationale, with an explanation for how the accommodations will ease the impact of the disability on the particular task in question. The most frequently requested test accommodations are extra time and a separate or distraction-free room. However, there is little empirical evidence to indicate what types of accommodations are most effective or appropriate for those with ADHD.

Bipolar Disorder and ADHD: Reciprocal Comorbid Conditions

Bipolar disorder is associated with substantial morbidity; there is often a very long lag time from the onset of symptoms to its accurate diagnosis and treatment (eg, 5–10 years). There can be a variety of initial symptoms, with depressed mood/hopelessness and mania/hyperactivity being the most frequently reported.[49] Other initial symptoms include insomnia, mood swings, anger/irritability, and delusions/paranoia. Depressive symptoms tend to predominate in patients with bipolar disorder, accounting for more than half of the time that patients spend with affective symptoms.[50]

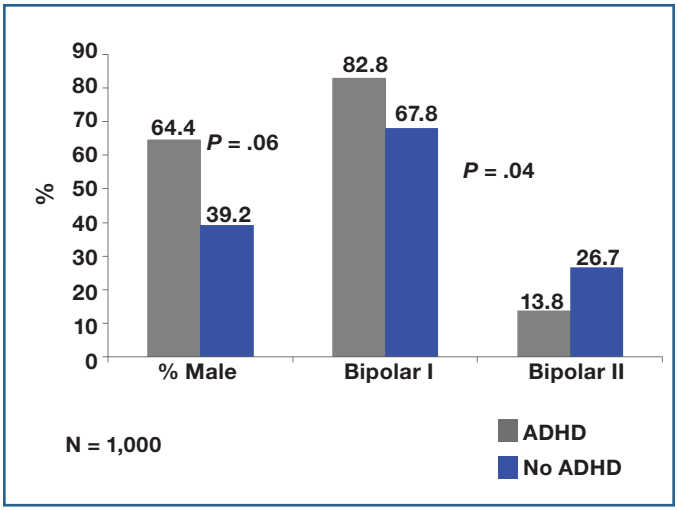

Figure 10. ADHD and bipolar disorder comorbidity.

Comorbid ADHD and bipolar disorder is common. Surveys suggest that 60% to 90% of children and adolescents with bipolar disorder have ADHD and 12% to 17% of children with ADHD develop bipolar disorder.[51-53] ADHD comorbidity is also common in adults with bipolar disorder.[54] In one study involving 1000 adults with bipolar disorder, the lifetime prevalence of ADHD was 9.5%, with 5.9% having a current diagnosis of ADHD.[54] This study found that patients with bipolar disorder and ADHD were more likely male (64.4% vs 39.2%; *P* = .06) and more likely to have bipolar type 1 (82.8% vs 67.8%; *P* = .04) and an earlier onset of mood disorder (13.9 years vs 18 years (*P* = .0001) compared with patients with bipolar disorder and no ADHD (**Figure 10**). Patients with ADHD/bipolar comorbidity also had more symptoms at study entry (eg, depression, hypomania, mania, mixed mood), worse functioning, more adverse lifetime events (eg, manic episodes, suicide attempts, violence, legal problems), and more SUD compared with bipolar individuals without ADHD.[54]

Treatment of comorbid ADHD and bipolar disorder is not well studied. One trial with 40 children and adolescents with comorbid ADHD/bipolar disorder evaluated the use of mixed amphetamine salts for the treatment of ADHD symptoms after patients had achieved mood stabilization with divalproex sodium.[55] Treatment with

divalproex sodium effectively reduced manic symptoms (ie, ≥50%) in 32 patients, but only 3 experienced a significant improvement in ADHD symptoms. For the 30 patients who entered the placebo-controlled phase, mixed amphetamine salts were significantly more effective than placebo for reducing ADHD symptoms.[55] Although promising, it is unclear whether co-treatment is indicated for patients with comorbid ADHD/bipolar disorder. Randomized, controlled trials are clearly needed to elucidate the role of pharmacotherapy for this debilitating comorbidity.

Cognitive-Behavioral Treatment of Adult ADHD

Because not all patients adequately respond to medication or have adverse effects, adjunctive CBT can be a useful adjunct or alternative treatment approach. Furthermore, because many patients with ADHD have underdeveloped "meta-cognitive" skills, there is a need to address ingrained, maladaptive behavior patterns. CBT is a therapeutic approach designed to change behavior, change cognitions, and impart skills. Specific strategies for behavioral and cognitive interventions are summarized in **Table 1**.

Table 1. Behavioral and cognitive strategies for the treatment of ADHD.

Strategies – Behavioral

- Learning explicit skills
  - How to use a planner, set up a filing system
- Practicing contingent self-reinforcement
- Breaking down complex tasks into manageable parts
- Counteracting steeper delay-of-reinforcement gradient by making distant rewards more salient
- Manipulating environment to minimize distraction
- Developing habits via intensive practice, group support, and positive reinforcement

Strategies – Cognitive

- Impart "rules" of daily scheduling, prioritizing, organization
- Develop adaptive cognitions to facilitate task initiation, completion, and planning
- "Mantras" (axioms)
  - To self-cue the application of the behavioral strategies
  - To promote maintenance
- Use traditional CBT methods to combat demoralization/depression, anxiety, and perfectionism

CBT is a therapeutic approach designed to change behavior, change cognitions, and impart skills

There are several components to the successful design of a CBT treatment regimen. The regimen should be practical and easy to assimilate, teach new meta-cognitive skills, and assimilate new behaviors in all activities of daily life in a way that becomes "habitual." The regimen should also address impairing self-attributions, have the ability to be replicated and researched, and include both in-session and home exercises.

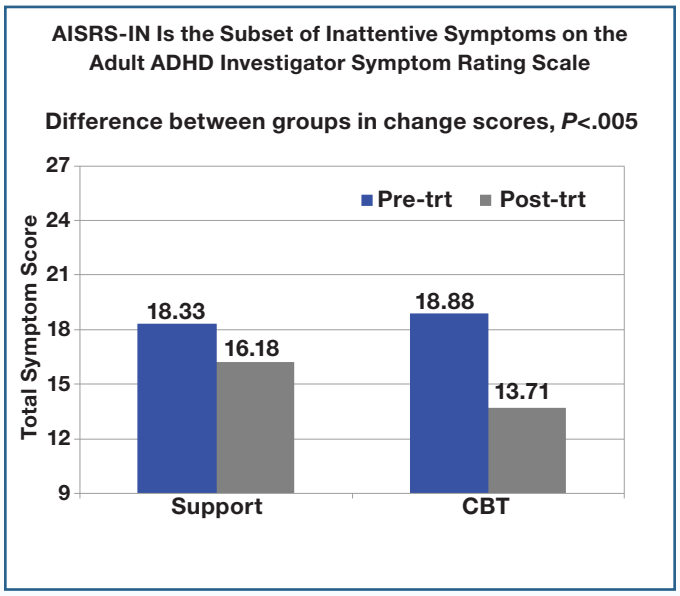

Figure 11. Effect of CBT on symptoms of ADHD.

A recent study funded by the National Institutes of Mental Health[26] evaluated the efficacy of a 12-week manualized CBT group intervention[56] designed to enhance time management, organization, and planning in adults with ADHD.[26] Eighty-eight adult patients were randomly assigned to either CBT or supportive psychotherapy. CBT was associated with significant reductions in inattentive symptoms compared with the support group. This included significantly greater improvement in the Adult ADHD Structured Interview for DMS-IV–Inattentive symptoms (AISRS-IN) in the CBT group (**Figure 11**). Similar results were observed for the Conners' Adult ADHD Rating Scale (CAARS) Inattention Scale, with significantly greater improvement in CBT-treated patients. Importantly, the response to CBT was not influenced by the use of concomitant medication.

Another recent study compared 12 individual sessions of either CBT or relaxation training with educational support in 86 adults with ADHD who had persistent symptoms despite the use of medication.[45] Patients who

were randomized to CBT achieved significantly better scores on the Clinical Global Impression scale and an ADHD rating scale, compared with those in the relaxation group.[45] Responders to CBT were able to maintain the improvement in ADHD through at least 12 months of follow-up.

Although CBT appears to be a useful adjunctive therapy for the treatment of ADHD, additional research is required to further define its role. Future studies should evaluate the value of longer treatment regimens (eg, 16 weeks plus booster sessions). Longer-term follow-up of outcomes is also required to compare the effects of maintenance CBT with the effects of ADHD medication. Studies are also required to elucidate and differentiate the mechanisms of action of CBT compared with that of medication. In addition, neuroimaging studies would be useful to assess whether CBT-related changes can be identified and possibly to predict response.

Cardiovascular Safety of ADHD Medication Treatments

In 2006, based on postmarketing reports of sudden cardiac death (SCD), an FDA advisory committee recommended a "black box" warning on the risk of cardiovascular events with stimulants. However, subsequent review by a separate advisory committee reversed the decision and instead mandated that manufacturers develop and distribute patient medication guides warning of cardiovascular and psychiatric risks. The difficulty with making these recommendations underscores the difficulty in sorting out drug-induced risk from that due to other causes (baseline risk, exercise-induced risk). All stimulants and the nonstimulant atomoxetine produce modest increases in blood pressure and heart rate,[57] and it is possible that even these small increases in cardiovascular parameters may increase risk across a large population, especially in adults. Thus, there is a need to screen adults with ADHD for cardiovascular safety for potential cardiovascular risk factors.

The cardiovascular risk associated with stimulants is low, and the nature of risk can be anticipated

Several studies have evaluated the risk for cardiovascular events, including sudden death in patients receiving stimulants. Although there is a biologic basis for an increased risk of cardiovascular events (ie, increased catecholaminergic activity), there is no compelling evidence of stimulant-induced risk for catastrophic events.[58] Based on available evidence and accumulated experience, the American Heart Association guidelines state that there is no compelling evidence that indicates a need to change therapy in successfully treated patients who tolerate their current medication regimens.[59] However, for individuals with preexisting family or personal history of SCD risk factors, or evidence of structural cardiac abnormalities, there is the potential for increased risk. In these cases, more extensive evaluation is required.[59]

Clinicians should screen for pre-existing history and symptoms of cardiac dysfunction in all patients, evaluate and consult as appropriate, and approach treatment with caution in patients deemed to be at increased risk. In some cases, this may mean forgoing treatment; in others, it may mean undertaking treatment in collaboration with a cardiology consultant.

For the most part, the cardiovascular risk associated with ADHD medication treatments is low and the degree of risk can be anticipated by pretreatment screening. An electrocardiogram (ECG) can detect a majority of abnormalities, and there is an emerging consensus in favor of wider screening of children and adolescents with ECG (especially athletes). Many believe that the benefits of screening generally outweigh the potentially adverse consequences. Although it is not required that all patients have a pretreatment ECG or other laboratory tests, clinicians should have a low threshold for recommending pretreatment cardiac work-up.

Misuse and Abuse of Stimulants Among US College Students

Misuse of a prescribed medication is defined as use for a reason or at a dosage other than that for which it was prescribed, with the patterns of misuse not necessarily leading to disability or dysfunction. *Illicit use* is defined as use of a medication without a prescription. *Abuse* is defined as use outside normally accepted standards of use (eg, euphoric effects) that results in disability/dysfunction. Stimulant misuse and diversion is common among ADHD patients, primarily among those with comorbid conduct disorder or SUD (**Figure 12**).[60] A survey of 9161 undergraduates found a lifetime prevalence of illicit stimulant use of 8.1%, with 5.4% reporting use within the last year.[61] This study found that illicit stimulant use was correlated with alcohol and other drug use. Males tend to have higher rates than females, and rates vary between schools and among racial groups. The major motives for the illicit use of stimulants are to improve attention, perform better on tests, improve study habits, stay awake, and as a party drug.

The College Life study is an ongoing longitudinal study designed to identify trends in prescription drug misuse among college students.[62] This study has found a 30% cumulative prevalence of the use of prescription stimulants during the first 4 years of college. It also found a clear longitudinal association between nonmedical use and declines in academic performance. Another study of 483

college students found that 35.8% diverted a medication at least once, with sharing and selling of prescription medications the most common type of diversion.[63] Stimulants were diverted at rate of 61.7% in this study. A study of fraternity members at the University of Kentucky found that 90% reported stimulants as "easy" or "very easy" to obtain and 89% thought that stimulants were "not dangerous at all" or only "slightly dangerous."[64]

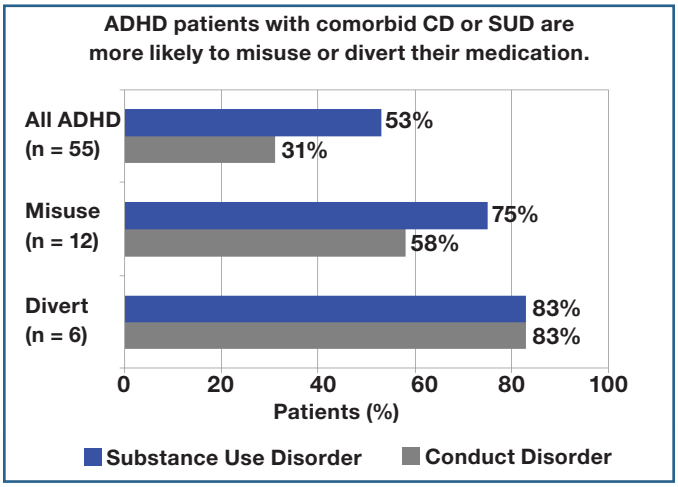

Figure 12. Characteristics of ADHD patients who misuse or divert medication.[60]

There are a number of factors that contribute to the rise in nonprescription stimulant use. These include precollege access to prescription drugs, greater availability of prescription drugs, higher rates of ADHD diagnosis in young adults, increased pressures to achieve in college, the perception that "everybody does it," more frequent recreational use, and marketing/media messages. Cultural expectations and norms (ie, casual acceptance of stimulant use) and the consumer marketing of pharmaceuticals also influence prescription drug misuse.

The major motives for the illicit use of stimulants are to improve attention, perform better on tests, improve study habits, stay awake, and as a party drug

Misuse of stimulants is a significant public health concern. Health risks include cardiovascular events (eg, SCD, heart attack, stroke, hypertension), psychiatric events (eg, psychosis, delirium, mania, anxiety, insomnia, depression), amphetamine intoxication (ie, maladaptive behavioral or psychological changes), stimulant withdrawal syndrome, and interactions with other substances (eg, medications, alcohol, recreational drugs).

There are several strategies for minimizing misuse/abuse of stimulants. These include:

- Conduct a comprehensive assessment of ADHD complaints and carefully evaluate patients for risk of medication misuse
- Rule out faking or simulation of ADHD symptoms
- Choose the most appropriate treatment (eg, long-acting stimulants)
- Educate patients/families about the risks of taking stimulants on college campuses and about ways to reduce potential misuse and abuse
- Use consent forms and documentation in the medical record
- Keep track of pills and refills
- Obtain urine toxicology frequently

Clinicians should also have a high suspicion regarding prescription drug abuse potential. Red flags include a demand for immediate-release stimulants, repeatedly discordant pill counts, frequently lost prescriptions, and requests to increase dosage. Colleges and universities also need to play an active role by developing policies/practices to educate students about risks of stimulant misuse/abuse and by imposing sanctions on students who divert medications.

Professional societies should intervene when physicians prescribe stimulant medications with insufficient documentation or inadequately monitor usage.

Conclusions

The assessment and treatment of adult ADHD is challenging, but these presentations illustrate some of the recent advances in our understanding of ADHD and its complications. The comorbidity of ADHD with various disorders (eg, bipolar disorder, SUD, eating disorders) complicates the clinical presentation and requires special management considerations. The persistence of ADHD into adulthood and the associated educational, workplace, social, and functional impairments makes the lifetime management of the disorder an important objective. Effective treatments (both pharmacologic and nonpharmacologic) are available, but an understanding of the issues involved in the assessment and management of the disorder is crucial to optimizing outcomes.

References

1. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.
2. Oosterlaan J, Scheres A, Sergeant JA. Which executive functioning deficits are associated with AD/HD, ODD/CD and comorbid AD/HD + ODD/CD. *J Abnorm Child Psychol*. 2005;33(1):69-85.
3. Nigg JT, Casey B. An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. *Dev Psychopathol*. 2005;17(3):785-806.
4. Barkley RA, Murphy KR. Impairment in occupational functioning and adult DHD: the predictive utility of executive function (EF) ratings vs EF tests. *Arch Clin Neuropsychol*. 2010;25(3):157-173.
5. Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder*. Am J Psychiatry.* 2001;158(7):1052-1057.
6. Ogdie MN, Macphie IL, Minassian SL, et al. A genome wide scan for attention-deficit/hyperactivity disorder in an extended sample: suggestive linkage on 17p11. *Am J Hum Genet*. 2003;72(5):1268-1279.
7. Zhou K, Dempfle A, Arcos-Burgos M, et al. Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(8):1392-1398.
8. Lowe N, Kirley A, Mullins C, et al. Multiple marker analysis at the promoter region of the DRD4 gene and ADHD: evidence of linkage and association with the SNP-616. *Am J Med Genet B Neuropsychiatr Genet.* 2004;131B(1):33-37.
9. Corradini I, Verderio C, Sala M, et al. SNAP-25 in neuropsychiatric disorders. *Ann N Y Acad Sci*. 2009;1152:93-99.
10. McGough JJ, McCracken JT, Loo SK, et al. A candidate gene analysis of methylphenidate response in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(12):1155-1164.
11. Kirley A, Lowe N, Hawi Z, et al. Association of the 480 bp DAT 1 allele with methylphenidate response in a sample of Irish children with ADHD. *Am J Med Genet B Neuropsychiatr Genet.* 2003;121B(1):50-54.
12. McGough J, McCracken J, Swanson J, et al. Pharmacogenetics of methylphenidate response in preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2006;45(11):1314-1322.
13. Polanczyk G, Zeni C, Genro JP, et al. Association of the adrenergic alfa2A receptor gene with methylphenidate improvement of inattentive symptoms in children and adolescents with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry.* 2007;64(2):218-224.
14. Michelson D, Read HA, Ruff DD, et al. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2007;46(2):242-251.
15. Klingberg T, Forssberg H, Westerberg H. Training of working memory in children with ADHD. *J Clin Exp Neuropsych*. 2002;24(6):781-791.
16. Klingberg T, Fernell E, Pernille J, et al. Computerized training of working memory in children with ADHD-a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2005;44(2):177-186.
17. McNab F, et al. Changes in cortical dopamine D1 receptor binding associated with cognitive training. *Science*. 2009;323(5915):800-802.
18. Gevensleben H, Holl B, Albrecht B, et al. Is neurofeedback an efficacious treatment for ADHD? A randomized controlled clinical trial. *J Child Psychol Psychiatry.* 2009;50(7):780-789.
19. 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(4):524-540.
20. Barkley RA, Murphy KR, Kwasnik. Motor vehicle driving competencies and risks in teens and young adults with attention deficit hyperactivity disorder. *Pediatrics.* 1996;98(6 Pt 1):1089-1095.
21. Millstein RB, Wilens TE, Biederman J, Spencer TJ. Presenting ADHD symptoms and subtypes in clinically referred adults with ADHD. *J Atten Disorder*. 1997;2:159-166.
22. Murphy K, Adler LA. Assessing attention-deficit/hyperactivity disorder in adults: focus on rating scales. *J Clin Psychiatry.* 2004;65 Suppl 3:12-17.
23. Adler LA, Shaw D, Sitt D, et al. Issues in the diagnosis and treatment of adult ADHD by primary care physicians. *Primary Psychiatry.* 2009;16:57-63.
24. Siedman LJ, Doyle A, Fried R, et al. Neuropsychological function in adults with attention-deficit/hyperactivity disorder. *Psychiatr Clin North Am*. 2004;27(2):261-282.
25. Biederman J, Petty C, Fried R, et al. Impact of psychometrically defined deficits of executive functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry.* 2006;163(10):1730-1738.

26. Solanto MV, Marks DJ, Wasserstein J, et al. Efficacy of meta-cognitive therapy for adult ADHD. *Am J Psychiatry.* 2010;167(8):958-968.

27. Biederman J, Seidman LJ, Petty CR, et al. Effects of stimulant medication on neuropsychological functioning in young adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2008;69(7):1150-1156.

28. Brown TE, Holdnack J, Saylor K, et al. Effect of atomoxetine on executive function impairments in adults with ADHD. *J Atten Disord*. 2009;15(2):130-138.

29. Maniadaki K, Sonuga-Barke E, Kakouros E, et al. Parental beliefs about the nature of ADHD behaviours and their relationship to referral intentions in preschool children. *Child Care Health Dev*. 2007;33(2):188-195.

30. Robin AL. Family intervention for home-based problems of adolescents with attention-deficit-hyperactivity disorder. *Adolesc Med State Art Rev*. 2008;19(2):268-277, ix.

31. Law J, Plunkett C, Taylor J, et al. Developing policy in the provision of parenting programmes: integrating a review of reviews with the perspectives of both parents and professionals. *Child Care Health Dev*. 2009;35(3):302-312.

32. Polanczyk G, de Lim MS, Horta BL, et al. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry.* 2007;164(6):942-948.

33. Mikami AY, Hinshaw SP, Patterson KA, Lee JC. Eating pathology among adolescent girls with attention-deficit/hyperactivity disorder. *J Abnorm Psychol*. 2008;117(1):225-235.

34. Molina BS, Hinshaw SP, Swanson JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry*. 2009;48(5):484-500.

35. Mikami AY, Hinshaw SP, Arnold LE, et al. Bulimia nervosa symptoms in the multimodal treatment study of children with ADHD. *Int J Eat Disord*. 2010;43(3):248-259.

36. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163(4):716-723.

37. Wilens TE, Biederman J, Mick E. Does ADHD affect the course of substance abuse? Findings from a sample of adults with and without ADHD. *Am J Addict*. 1998;7(2):156-163.

38. Volkow ND, Wang GJ, Kollins SH, et al. Evaluating dopamine reward pathway in ADHD: clinical implications. *JAMA.* 2009;302(10):1084-1091.

39. 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(1):179-185.

40. Fredericks EM, Kollins SH. Assessing methylphenidate preference in ADHD patients using a choice procedure. *Psychopharmacology*. 2004;175(4):391-398.

41. Wilens TE, Adamson J, Monuteaux MC, et al. Effect of prior stimulant treatment for attention-deficit/hyperactivity disorder on subsequent risk for cigarette smoking and alcohol and drug use disorders in adolescents. *Arch Pediatric Adolesc Med*. 2008;162(10):916-921.

42. Collins SL, Levin FR, Foltin RW, et al. Response to cocaine, alone and in combination with methylphenidate, in cocaine abusers with ADHD. *Drug Alcohol Depend*. 2006;82(2):158-167.

43. Riggs P, Winhusen TM. Randomized controlled trial of osmotic release methylphenidate (OROS-MPH) attention deficit hyperactivity disorders in adolescents with substance use disorders. American Academy of Addiction Psychiatry 20th Annual Meeting. Los Angeles, CA; December 3-6, 2009.

44. Wilens TE, Adler LA, Weiss MD, et al; Atomoxetine ADHD/SUD Study Group. Atomoxetine treatment of adults with ADHD and comorbid alcohol use disorders. *Drug Alcohol Depend*. 2008;96(1-2):145-154.

45. Safren SA, Sprich S, Mimiaga MJ, et al. Cognitive behavioral therapy vs relaxation with educational support for medication-treated adults with ADHD and persistent symptoms: a randomized controlled trial. *JAMA.* 2010;304(8):875-880.

46. Able SL, Johnston JA, Adler LA, Swindle RW. Functional and psychosocial impairment in adults with undiagnosed ADHD. *Psychol Med*. 2007;37(1):97-107.

47. Faraone SV, Spencer TJ, Montano CB, Biederman J. Attention-deficit/hyperactivity disorder in adults: a survey of current practice in psychiatry and primary care. *Arch Intern Med*. 2004;164(11):1221-1226.

48. Murphy K. ADHD documentation for test accommodations under the ADA: clarifying the confusion. *The ADHD Report*. 2004;12(5):1-5.

49. Lish JD, Dime-Meenan S, Whybrow PC, et al. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J Affect Disord*. 1994;31(4):281-294.

50. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psych.* 2003;60(3):261-269.

51. West SA, McElroy SL, Strakowski SM, et al. Attention deficit hyperactivity disorder in adolescent mania. *Am J Psychiatry.* 1995;152(2):271-273.

52. Geller B, Bolhofner K, Craney JL, et al. Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. *J Am Acad Child Adolesc Psychiatry.* 2000;39(12):1543-1548.

53. Wozniak J, Biederman J, Kiely K, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry.* 1995;34(7):867-876.

54. Nierenberg AA, Miyahara S, Spencer T, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol Psychiatry*. 2005;57(11):1467-1473.

55. Scheffer RE, Kowatch RA, Carmody T, Rush AJ. 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(1):58-64.

56. Solanto MV. *Cognitive-behavioral therapy for adult ADHD: targeting executive dysfunction*. New York, NY: Guilford Press; 2011.

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

58. Wilens TE, Prince JB, Spencer TJ, Biederman J. Stimulants and sudden death: what is a physician to do? *Pediatrics*. 2006;118(3):1215-1219.

59. Vetter VL, Elia J, Erickson C, et al; American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee; American Heart Association Council on Cardiovascular Nursing. Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder [corrected]: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. *Circulation.* 2008;117(18):2407-2423.

60. Wilens J, Gignac M, Swezey A, et al. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. *J Am Acad Child Adolesc Psychiatry*. 2006;45(4):408-414.

61. Teter CJ, McCabe SE, Cranford JA, et al. Prevalence and motives for illicit use of prescription stimulants in an undergraduate student sample. *J Am Coll Health*. 2005;53(6):253-262.

62. Arria AM, DuPont RL. Nonmedical prescription stimulant use among college students: shy we need to do something and what we need to do. *J Addict Dis*. 2010;29(4):417-426.

63. Garnier LM, Arria AM, Caldeira KM, et al. Sharing and selling of prescription medications in college student sample. *J Clin Psychiatry.* 2010;71(3):262-269.

64. DeSantis A, Noar SM, Webb EM. Nonmedical ADHD stimulant use in fraternities. *J Stud Alcohol Drugs*. 2009;70(6):952-954.

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Activity Evaluation Form **Highlights from a Conference – *ADHD: Current Concepts and Future Developments***

Instructions for Completion

To obtain continuing education (CE) credit within 4 weeks following receipt of a completed form, please: 1) Complete the attached self-assessment and evaluation by June 6, 2012. 2) Fax the form to 215-337-0959 or mail completed form to MediCom Worldwide, Inc., 101 Washington Street, Morrisville, PA 19067. Remember to fax or mail both pages of the form. 3) All participants must achieve a minimum score of 70% on the self-assessment portion of the form to qualify for CE credit. 4) The participant will be mailed his/her CE certificate within 4 weeks following receipt of the completed, qualified form.

Participant Information

Name:_____

Mailing Address:_____

_____

City:_____ State:_____ Zip:_____

License Number/State: _____ Pharmacists Only *Required*: DOB (MMDD): _____ NAB e-profile ID: _____

Professional Degree:

○ MD ○ DO ○ PharmD ○ RPh ○ RN ○ LPN ○ NP ○ PhD ○ PA ○ Other:_____

Specialty: _____ Years in practice: _____ Number of ADHD patients seen/week: _____

☐ Please contact me regarding upcoming medical education opportunities.

Activity Evaluation

Please rate the activity by filling in the most appropriate circle.

	(5) Excellent (4) Good (3) Satisfactory (2) Fair (1) Poor	5	4	3	2	1
1. Overall content		○	○	○	○	○
2. Format		○	○	○	○	○

How well did this activity achieve its educational objectives?

Please use the following scale. (5) Strongly Agree (4) Agree (3) Neutral (2) Disagree (1) Strongly Disagree	5	4	3	2	1
3. Increase clinical inquiries and screening for ADHD in adolescent and adult patients to improve detection rates	○	○	○	○	○
4. Apply criteria to definitively diagnose ADHD and identify potential comorbid conditions such as mood disorders and substance use disorders in adolescents and adults	○	○	○	○	○
5. Understand the role of pharmacotherapy and nonpharmacotherapy modalities of treatment in the management of adolescent and adult ADHD patients	○	○	○	○	○
6. Develop a strategy for tailoring individualized, comprehensive treatment plans and monitoring for medication adherence to effectively treat and manage ADHD in adolescent and adult patients	○	○	○	○	○
7. Review potential cardiovascular risks associated with some ADHD treatments and understand how to conduct a thorough clinical review to screen for at-risk patients	○	○	○	○	○
8. Understand the value of neuropsychological tests and rating scales, along with performing a thorough clinical interview utilizing *DSM-IV* criteria	○	○	○	○	○
9. Summarize the benefits of cognitive-behavioral therapies to improve outcomes for ADHD patients	○	○	○	○	○

	Yes	No
10. Do you feel the activity was useful to you in your practice setting?	○	○
11. Do you feel that fair balance was maintained for all therapeutic options?	○	○
12. As a result of participation in this activity, do you plan on making any changes in your practice?	○	○
13. If yes, please identify at least one change you plan on making _____		
14. Would you participate in future self-study activities?	○	○

15. How long did it take you to complete this activity? ○ 60 minutes ○ 75 minutes ○ 90 minutes

Please provide detailed comments and suggestions for future activities. _____

Self-Assessment Questions

1. Despite the linkage of ADHD to EF deficits, data indicate that only _____ of cases of ADHD fall in the impaired range of EF tests.
   - ○ a. 10% to 25%
   - ○ b. 25% to 40%
   - ○ c. 35% to 50%
   - ○ d. 55% to 70%

2. Which of the following levels of the 6-level extended phenotype of EF is NOT disrupted in patients with ADHD?
   - ○ a. Pre-executive
   - ○ b. Adaptive/self-reliant
   - ○ c. Tactical/interactive
   - ○ d. Utilitarian/outcomes

3. Management of EF deficits in young adults with ADHD includes _____.
   - ○ a. Nonstimulants
   - ○ b. Stimulants
   - ○ c. Psychosocial/cognitive-behavioral therapy
   - ○ d. All of the above

4. What is the peak age of diagnosis of ADHD?
   - ○ a. 4 to 5 years
   - ○ b. 6 to 8 years
   - ○ c. 9 to 11 years
   - ○ d. 12 to 14 years

5. ADHD is often comorbid with which of the following conditions?
   - ○ a. Bipolar disorder
   - ○ b. Eating disorders
   - ○ c. Substance abuse
   - ○ d. All of the above

6. Which of the following medications may be particularly effective for abstinent alcohol-dependent individuals with ADHD?
   - ○ a. Atomoxetine
   - ○ b. Bupropion
   - ○ c. Desipramine
   - ○ d. Methylphenidate

7. Proper diagnosis of ADHD in adults should be based on which of the following?
   - ○ a. Findings on a clinical interview
   - ○ b. Neuropsychological test scores
   - ○ c. Results of the Barkley Current Symptoms Scale
   - ○ d. None of the above

8. Which condition must be met for a patient with ADHD to potentially be eligible for coverage under the Americans with Disabilities Act Amendments Act?
   - ○ a. A specific level of symptom severity
   - ○ b. Current and credible documentation by a qualified professional
   - ○ c. Diagnosis according to *DSM-IV* criteria
   - ○ d. Documentation of symptoms using an ADHD rating scale

9. In a study of patients with bipolar disorder, those with comorbid ADHD and bipolar disorder had _____ compared with those with bipolar disorder only.
   - ○ a. More symptoms at study entry
   - ○ b. Better functioning
   - ○ c. Fewer adverse lifetime events
   - ○ d. Fewer cases of substance abuse disorder

10. It is estimated that ADHD may affect more than _____ million adults in the United States.
    - ○ a. 6
    - ○ b. 7
    - ○ c. 9
    - ○ d. 10

I certify that I have completed this educational activity as designed.

Signature:_____ Date:_____