New Developments in the Treatment of Attention-Deficit/Hyperactivity Disorder in Primary Care

This ACADEMIC HIGHLIGHTS section of The Primary Care Companion to The Journal of Clinical Psychiatry *presents the highlights of the series of planning teleconferences "New Developments in the Treatment of Attention-Deficit/Hyperactivity Disorder," which was held in May 2005. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Cephalon, Inc.*

The series of planning teleconferences was chaired by ***Joseph Biederman****, M.D., Massachusetts General Hospital and the Department of Psychiatry, Harvard Medical School, Boston. The faculty were* ***Amy F. T. Arnsten****, Ph.D., Department of Neurobiology, Yale University School of Medicine, New Haven, Conn.;* ***Stephen V. Faraone****, Ph.D., Medical Genetics Research Program and the Department of Psychiatry, SUNY Upstate Medical University, Syracuse, N.Y.;* ***Alysa E. Doyle****, Ph.D., Massachusetts General Hospital and the Department of Child Psychiatry, Harvard Medical School, Boston;* ***Thomas J. Spencer****, M.D., Pediatric Psychopharmacology Unit, Psychiatry Service, Massachusetts General Hospital and the Department of Psychiatry, Harvard Medical School, Boston;* ***Timothy E. Wilens****, M.D., the Pediatric Psychopharmacology Unit, Massachusetts General Hospital and Harvard Medical School, Boston;* ***Margaret D. Weiss****, M.D., Ph.D., the Department of Psychiatry, University of British Columbia, Vancouver, Canada;* ***Steven A. Safren****, Ph.D., Massachusetts General Hospital and the Department of Psychiatry, Harvard Medical School, Boston; and* ***Larry Culpepper****, M.D., M.P.H., Department of Family Medicine, Boston University, Boston, Mass.*

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Overview: Causes, Course, and Treatment of ADHD

Chair Joseph Biederman, M.D., stated that attention-deficit/hyperactivity disorder (ADHD) is a common, early-onset neuropsychiatric disorder that affects an estimated 3% to 7% of school-aged children[1] and 4% of adults.[2,3] ADHD is characterized by inattention, hyperactivity, and impulsivity—all of which can lead to substantial social, academic, and occupational impairment.

The presumed pathophysiology of ADHD is an abnormality in central dopaminergic and noradrenergic tone.[4] Thus, pharmacotherapies that have been shown to be effective in both children and adults have been those affecting these 2 neurotransmitters.[5,6] Despite the fact that stimulant medications, such as methylphenidate, pemoline, and dextroamphetamine and mixed amphetamine salts have been proven safe and effective for the treatment of ADHD, an estimated 30% to 50% of all children and adults with ADHD either do not respond to or do not tolerate treatment with stimulants.[7] Recently, the nonstimulant medication atomoxetine was approved for use in both children and adults for the treatment of ADHD. Atomoxetine is a potent inhibitor of presynaptic norepinephrine transport and is generally free of effects on other noradrenergic receptors or other neurotransmitter receptors or systems.

Dr. Biederman explained that a growing body of new information on ADHD is driving the development of new options for treating patients with ADHD. Advances in our understanding of the neurobiology of ADHD, the genetic and environmental factors associated with ADHD, the role of impairments in executive functions in ADHD, comorbid diagnosis research, the mechanism of action of the various agents used for treating ADHD, and cognitive-behavioral approaches to treating ADHD have given rise to interest in nonstimulant therapies, such as guanfacine, which is an α_2-adrenergic receptor agonist, and a new formulation of modafinil, which appears to reduce the core symptoms of ADHD via the same mechanism by which it improves wakefulness. In addition, transdermal technology has led to the development of a methylphenidate patch that was recently approved by the FDA. The patch allows continuous medication release throughout the day and eases the challenges of timely oral delivery to school-aged children.

Dr. Biederman explained that as the causes and course of ADHD are better understood, newer and more selective medications are being developed for ADHD. Primary care physicians will play a key role in helping to build a therapeutic alliance among the patient, family, and caring mental health professionals with expertise in the treatment of ADHD.

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Fundamentals of ADHD: Circuits and Pathways

Amy F. T. Arnsten, Ph.D., stated that ADHD is associated with alterations in the prefrontal cortex (PFC) and in its connections to the striatum and cerebellum. Understanding the higher association cortices can provide important insights into the complex symptomatology of ADHD. Dr. Arnsten reviewed the function of the higher association cortices relevant to ADHD, the connections of these cortical areas to the basal ganglia and cerebellum, and the powerful modulation of these circuits by dopamine and norepinephrine.

Dr. Arnsten explained that the PFC regulates behavior, sustains attention over a delay, divides attention, and inhibits distraction. Lesions to this part of the brain produce distractibility, poor concentration and organization, impulsivity, forgetfulness, locomotor hyperactivity, and poor planning—all symptoms associated with ADHD.[1]

The parietal and temporal association cortices, as well as the PFC, project to the caudate nucleus as part of the cognitive circuit to the basal ganglia and cerebellum. The basal ganglia may be important in the planning, selection, initiation, and execution of thoughts. The cerebellum may have a role in cognitive function and has been shown to be consistently smaller in children with ADHD.[2] The basal ganglia are powerfully modulated by dopamine, and the cerebellum is heavily innervated by norepinephrine. Thus, Dr. Arnsten concluded, genetic alterations that affect catecholamine actions may alter basal ganglia and cerebellar functioning, and changes in catecholamines have profound effects on the functioning of the PFC.

Dr. Arnsten then explained the role of dopamine and norepinephrine in modulating these circuits. Dopamine acts at the D_1 and D_2 receptor families, and the PFC is rich in D_1-, D_4- and D_5-receptors. Modest levels of D_1 family receptor stimulation are essential to PFC function while high levels of dopamine release result in impaired working memory. Optimal levels of D_1-/D_5-receptor stimulation enhance working memory by reducing noise, while high doses have generally suppressive effects.[3] Norepinephrine acts at α_1-, α_2-, β_1-, β_2-, and β_3-adrenoceptors. Moderate levels of norepinephrine release have a critical beneficial influence on prefrontal function through actions at postsynaptic α_{2A}-adrenoceptors. Stimulation of these receptors improves working memory, lessens distractibility, and strengthens impulse control. At the cellular level, α_{2A}-adrenoceptor stimulation increases signals by inhibiting the production of cyclic adenosine monophosphate (cAMP). High levels of norepinephrine release impair PFC function through α_1 receptors coupled to protein kinase C.[4] Thus, α_1-agonists impair working memory,[5] whereas α_1-blockers have a protective effect on PFC cognitive abilities, preventing stress-induced PFC impairment.

Dr. Arnsten stated that the stimulants amphetamine and methylphenidate act to enhance the release and/or inhibit the reuptake of both dopamine and norepinephrine. Both likely contribute to the therapeutic effects through stimulation of D_1- and α_{2A}-receptors, respectively.

Dr. Arnsten summarized her comments by stating that optimal PFC function occurs with the moderate release of catecholamines, the increase of signals by norepinephrine α_{2A}-receptor stimulation, and the decrease of noise by the dopamine D_1-receptor. Catecholamines have powerful influences on the brain circuits that appear to be altered in ADHD. Therefore, medications that can optimize catecholamine transmission may normalize the function of these circuits and ameliorate ADHD symptomatology.

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Candidate Gene Studies of ADHD

Stephen V. Faraone, Ph.D., stated that ADHD is a complex neurobehavioral condition that has a high degree of heterogeneity. A growing body of behavioral and genetics literature has indicated that the development of ADHD may be attributed to both genetic and environmental factors. Family, twin, and adoption studies of ADHD provide evidence that genes are involved in mediating susceptibility to ADHD[1,2] and implicate several genes in the etiology of the disorder. Dr. Faraone presented a detailed analysis of the 8 genes for which the same variant has been studied in 3 or more case-control or family-based studies. Seven show statistically significant evidence of association with ADHD based on the pooled odds ratios across studies: the dopamine D_4 receptor gene (*DRD4*), the dopamine D_5 receptor gene (*DRD5*), the dopamine transporter gene (*DAT*), the dopamine β-hydroxy-

lase gene (*DBH*), the serotonin transporter gene (*5-HTT*), the serotonin receptor 1B gene (*HTR1B*), and the synaptosomal-associated protein 25 gene (*SNAP25*). For a complete review see Faraone et al.[1]

Pharmacogenetic studies investigate how gene variants influence medication response and have the potential to provide gene markers that will predict medication efficacy. Identification of these gene variants and how they influence drug response may elucidate the biological mechanisms of disease pathogenesis, thus stimulating developments of new therapeutic agents.

Looking ahead, Dr. Faraone stated that the evolving field of pharmacogenetics may someday enable clinicians to use genetics to identify individual patient characteristics and treat them accordingly.

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Executive Functions in ADHD

Alysa E. Doyle, Ph.D., reviewed the existing literature on the impairments in executive functions associated with ADHD. Despite a large literature on this topic, the core neuropsychological impairments underlying this disorder have not been fully resolved. Moreover, recent studies indicate that ADHD is best conceptualized as a neuropsychologically heterogeneous condition.

Neuropsychological Findings

Individuals with ADHD perform poorly on clinical neuropsychological tests of attention and executive functions that attempt to measure prefrontal cortex dysfunction.[1] The term *executive functions* refers to the higher cognitive processes that control self-regulation and goal-directed behavior such as response inhibition, working memory, abstract thinking, planning, organizing, attention shifting, and verbal fluency.[2] Popular theoretical models of ADHD have argued that specific aspects of executive dysfunction represent the core deficit in the condition, with the most widely discussed aspects being response inhibition and impaired working memory.[3]

Heterogeneity Within ADHD

Although executive functions weaknesses are prevalent in patients with ADHD, variability between studies and within ADHD samples indicates that normal executive functioning ratings cannot be used to make or rule out a diagnosis of ADHD. This caveat is due to the fact that not every subject with ADHD is impaired on every executive functions examination; some individuals with ADHD perform within the normal range on some or all of the measures.[4]

Normal-range performance may be due to several factors. One possibility is that measures of executive functions were developed to assess the effects of significant cerebral insults and may not capture mild cognitive impairments occurring within the context of development. Also, some individuals may have underlying impairments but may have learned compensatory strategies that allow them to use alternative resources to solve frontal system tasks. Another possibility is that executive function deficits may not be the core or only causal deficit underlying ADHD.[5,6] Dr. Doyle emphasized that these alternative mechanisms are important to consider in addition to executive deficits as neuropsychological mechanisms underlying ADHD, but research suggests that they are unlikely to represent single core deficits that account for all cases.

Potential Moderators of Neuropsychological Heterogeneity

Dr. Doyle emphasized that several possible factors, including family history, comorbid disorders, DSM-IV subtypes, and developmental differences, may be associated with the variability of performance on executive function measures. For instance, familial and nonfamilial cases of ADHD may differ neuropsychologically, with the former showing greater severity of impairments.[7] Additionally, the presence of comorbid disorders may exacerbate or modify the neuropsychological profile of patients with ADHD. Subjects with ADHD and comorbid learning disorders tend to exhibit deficits in executive functions.[8] Although the number of neuropsychological studies of other comorbidities in ADHD is limited, youths with ADHD and anxiety disorders show fewer severe deficits in response inhibition tasks but more severe deficits in working memory tasks than youths with only ADHD.[9]

Meta-analyses have not yielded strong evidence of neuropsychological differences between ADHD DSM-IV subtypes[10]; however, one study[11] documented greater difficulty with resistance to interference in patients with ADHD-Inattentive subtype compared to those with other subtypes.

Although there is a paucity of studies concerning developmental differences, adults, adolescents, and children with ADHD have all shown impairments in executive functions. However, the studies representing these samples are largely cross-sectional and, as a result, Dr. Doyle stated the need for longitudinal studies to better understand the development and course of neuropsychological impairments across the lifespan of individuals with ADHD.

Conclusion

An association exists between ADHD and deficits in response inhibition, working memory, and other domains of executive functioning. However, some individuals with ADHD perform within the normal range on tests of executive function, which may result from measurement issues, compensatory mechanisms, or ADHD, in some cases, arising from alternative deficits. Also, neuropsychological vari-

ability within ADHD populations may be moderated by factors such as family history of the disorder, comorbidity, symptom dimensions, and developmental stage. Taken as a whole, the literature indicates that this disorder may be best understood as a neuropsychologically heterogeneous condition.

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ADHD and Comorbidity

Thomas J. Spencer, M.D., stated that high rates of concurrent psychiatric and learning disorders have been documented among individuals with ADHD (Table 1).[1–5]

Mood Disorders

Comorbid mood disorders, such as major depression or bipolar disorder, have been found to occur in 15% to 75% of children and adolescents with ADHD.[1] In a 4-year follow-up,[6] lifetime rates of comorbid depression in children with ADHD increased from 29% at baseline to 45% at an average age of 15 years. Depressive symptoms include abnormal sleep patterns, weight changes, loss of pleasure, feelings of worthlessness or guilt, and suicidal preoccupation. The combination of these depressive symptoms and ADHD, if not recognized, may lead to increased disability, morbidity, and mortality. Dr. Spencer noted that an unusual feature of depression in youths with ADHD is the high rate of conversion to mania characterized by irritability, explosive mood, poor psychosocial functioning, high energy, and poor judgment.

Anxiety Disorders

Childhood anxiety disorders, such as separation anxiety disorder and selective mutism, are comorbid in 25% of youths with ADHD.[1] Juveniles and adults with anxiety disorders often display symptoms that overlap with those of ADHD, such as rumination, vigilant apprehension, agitation, tantrums, overdependence, and ritualistic behaviors.[7] Anxiety problems in childhood or adolescence can indicate considerable impairment in later adult functioning,[8] substantially exacerbating the ADHD.

Oppositional Defiant Disorder and Conduct Disorder

Oppositional defiant disorder is characterized by negative, hostile, and deviant behavior, whereas conduct disorder is a persistent and more severe disorder with habitual rule-breaking, aggression, destruction, lying, stealing, and truancy. In a 4-year study[9] of children with ADHD, a diagnosis of conduct disorder was almost always comorbid with oppositional defiant disorder. Furthermore, in the absence of conduct disorder, oppositional defiant disorder did not necessarily progress to conduct disorder, nor did it share the poor outcome of conduct disorder. Although the overlap of these 2 disorders is asymmetric,[9] oppositional defiant disorder has a prevalence rate of 35% to 65% and conduct disorder has a 10% to 20% prevalence rate in children and adolescents with ADHD.[2]

Table 1. Prevalence of Comorbid Disorders Present in Individuals With ADHD

Comorbid Disorders	Prevalence (%)
Mood[1]	15–75
Anxiety[1]	25
Oppositional defiant[2]	35–65
Conduct[2]	10–20
Developmental[3]	10–90
Tic[4]	50
Substance use[5]	20–40

Developmental Disorders

Developmental disorders include mental retardation, pervasive developmental disorders (e.g., autism), and specific developmental disorders (e.g., learning disabilities). Children with mental retardation and pervasive developmental disorders often have comorbid psychiatric disorders and behavioral problems resembling ADHD such as hyperactivity, aggressiveness, and distractibility. Also, children with ADHD exhibit problems associated with learning disabilities, such as requiring more tutoring, receiving lower grades, repeating more years of schooling, needing more special class placement,[3] and performing more poorly on intelligence and achievement tests than children without ADHD.[1] ADHD and learning disabilities have a 10% to 90% degree of overlap.[3]

Tic Disorders

The presence of a tic disorder does not necessarily contribute additional dysfunction to children with ADHD. One study[10] reported high remission rates of tic disorders and an overall limited impact on the course of ADHD. In contrast to the severe consequences of other comorbid disorders such as conduct, mood, and anxiety disorders, tic disorders minimally affect the overall outcome of ADHD.

Substance Use Disorders

Studies[11,12] show that young adults with ADHD disproportionately become involved with cigarettes, alcohol, and drugs compared with the general population. Adolescents and adults with ADHD become addicted to smoking at twice the rate and maintain addictions longer than individuals without ADHD.[13] Moreover, adults with ADHD and comorbid substance abuse tend to prefer drugs, especially marijuana, over alcohol.[13]

Conclusion

While ADHD is characterized by behavioral symptoms of inattention, hyperactivity, and impulsivity across the life cycle, comorbidity is a distinct clinical feature in both children and adults. Due to overlapping symptomatology, Dr. Spencer emphasized that it is often difficult to accurately diagnose ADHD versus mood, anxiety, conduct, oppositional defiant, or developmental disorders.

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Mechanism of Action of Agents Used for Treating ADHD

Timothy E. Wilens, M.D., stated that several stimulants and nonstimulants are effective in treating individuals with ADHD. Elucidating the various mechanisms of action of these ADHD medications may lead to better choices in matching potential responses to specific characteristics of individuals.

Stimulants

Efficacy of ADHD treatment is related to the pharmacokinetics and pharmacodynamics of the medication.[1] The 2 major processes related to the concentration of dopamine in the synapse are the exocytic release of dopamine and other neurotransmitters and carrier-mediated transport of catecholamines such as dopamine.[2] Three fundamental processes underlying the mechanisms of action of stimulants are release, uptake inhibition, and enzymatic inactivation of transmitters.[2] Stimulants block the reuptake of dopamine and norepinephrine into the presynaptic neuron and increase the release of monoamines.[2,3]

Amphetamine. The release actions and uptake-inhibiting actions of amphetamine[2] are mediated by the catecholamine uptake transporter and increase the concentration of synaptic dopamine.

Methylphenidate. Methylphenidate binds to the dopamine transporter protein, increasing synaptic dopamine and leading to the inhibition of dopamine reuptake.[2,4] The degree of uptake inhibition, baseline stimulation, and the environment appear to influence dopamine levels in methylphenidate-treated individuals.[5]

Nonstimulants

The noradrenergic system has been associated with modification of the higher cortical functions including attention, alertness, and vigilance. Attention and vigilance depend on adequate modulation by catecholamine neurotransmitters of the PFC on brain networks with a high distribution of noradrenergic neurons.

Atomoxetine. Atomoxetine has been shown to be effective in children, adolescents, and adults with ADHD.[6] This agent inhibits presynaptic norepinephrine reuptake[6] and increases dopamine in the PFC, which may be related to improvements in executive and other cognitive functioning.

Clonidine. The antihypertensive agent clonidine is being used more frequently in the treatment of ADHD, tics, and aggression,[7] especially in younger children. Clonidine has α-adrenergic agonist properties with both central and peripheral effects.[8] This agent interacts with several neurotransmitter systems, which may account for its diverse action on drug-withdrawal states, impulsivity, and cognition.[7,8]

Guanfacine. Guanfacine modulates presynaptic and postsynaptic norepinephrine activity that appears to be related to basal adrenergic tone. This agent is a potent agonist of the α_2-receptor, which results in heightened

PFC bloodflow, and improved working memory and executive functioning in patients with ADHD.[9]

Bupropion. Bupropion is pharmacologically distinct from any other available antidepressant. The mechanism of action of bupropion involves the reuptake inhibition of dopamine and norepinephrine, and has been shown to potentiate dopaminergic neurotransmission.[10]

Tricyclic antidepressants (TCAs). TCAs have demonstrated effectiveness against ADHD symptomatology in children and adults.[11] Specific TCAs such as imipramine and amitriptyline are more selective for the serotonin transporter; and desipramine, nortriptyline, and protriptyline are more selective for the norepinephrine transporter. Given the redundancy of activity with stimulants, TCAs may be additive or synergize stimulant effects pharmacodynamically.

Modafinil. Although mainly used to treat narcolepsy, this agent has effects on catecholaminergic neurotransmission, especially dopamine and norepinephrine. Whether these effects are related to modafinil's therapeutic effects in ADHD remains controversial.

Nicotinic agents. Cholinergic dysregulation, specifically in nicotinic cholinergic systems, may play a role in the pathophysiology of ADHD.[12] Dr. Wilens noted that patients with ADHD have an increased risk and earlier age at onset of nicotine use than individuals without ADHD.[13]

Conclusion

Commonalities exist in the various agents used in ADHD. Attenuation of central catecholaminergic neurotransmission appears fundamental in the amelioration of ADHD symptoms. Dr. Wilens reinforced that elucidating the various mechanisms of action of ADHD medications will undoubtedly be of major assistance in treating the disorder in the future.

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Effectiveness Outcomes in ADHD

Margaret D. Weiss, M.D., Ph.D., stated that pharmacotherapy alone or in conjunction with psychotherapy in the treatment of ADHD can improve patients' symptoms[1]; however, examining the evidence and selecting treatment options based on that evidence can be difficult. Dr. Weiss described the characteristics of efficacy studies and effectiveness studies as varying methods of collecting data that affect the outcomes of treatment recommendations for treating ADHD. She cited differences associated with the population sample, the practice setting, informant reliability, drug characteristics, and other outcome variables as important differences between efficacy studies and effectiveness studies.

First, efficacy research is focused on measuring change in the symptomatology of ADHD in a narrowly defined population, whereas effectiveness research is directed toward understanding the success of these treatments in practice in helping individuals not only with ADHD, but with their ability to function. Efficacy studies focus on populations that meet the full criteria for ADHD, whereas effectiveness studies determine whether patients who do not meet the full diagnostic criteria but still experience impairment can be treated successfully. In addition, patients in efficacy studies usually have only ADHD, whereas more than three quarters of clinical patients will have 1 or more comorbid disorders.[2]

Next, Dr. Weiss described differences in the practice setting. Efficacy studies[3,4] of ADHD treatment have shown increased patient response rates to medication when administered by researchers as opposed to community physicians. This affect limits physicians' capacity to infer that the outcomes found in these efficacy trials will be reproduced in the community. Effectiveness trials may reveal treatment procedures that will optimize care delivered by front-line physicians.

Efficacy studies are conducted using self-reports, reports from significant others or family, or clinician interviews. There is little interrater reliability among informants[5] because some individuals, especially children, do not recognize their own symptoms, family and friends may dismiss or deny them, and teachers may see different aspects of the disorder than parents. Effectiveness studies will target areas of functional impairment in life skills, learning, and social relationships, and so on. Dr. Weiss asserted that efficacy

studies focus on alleviating symptoms whereas effectiveness studies will allow doctors to determine more about how improvement in symptoms leads to improvement in the patient's capacity to function and his or her overall quality of life.

Turning her focus to medication, Dr. Weiss stated that efficacy studies indicate the success of medication in a controlled environment, while effectiveness studies show how well that drug works in the real-world patient population. Although multiple ADHD medications may perform equally in efficacy studies, this does not tell physicians about those patients with selective medication response. Effectiveness studies may help define individual characteristics that determine optimal pharmacotherapy management.

Finally, Dr. Weiss stated that the primary outcome variable in clinical efficacy trials is the significant improvement of disorder symptoms according to the effect size. Effectiveness studies may also measure such variables as changes in functioning, quality of life, times of impairment, and outcomes of other disorders or associated symptoms.

Dr. Weiss theorized that future study designs may combine the best aspects of practical clinical trials[6] and naturalistic observational study methods.

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Cognitive-Behavioral Approaches to ADHD Treatment in Adulthood

Steven A. Safren, Ph.D., stated that most adults who receive pharmacotherapy for ADHD experience some residual symptoms and functional impairment. Recommendations for treatment of ADHD in adults and adolescents, therefore, call for psychosocial intervention concomitant with medication.[1] Although psychopharmacology can ameliorate many of the core symptoms of ADHD such as attention difficulty, high activity, and impulsivity, it does not intrinsically provide patients with coping strategies associated with their functional impairment. Reviews of psychosocial intervention in addition to medication show that coupling the 2 methods can prevent the exacerbation of residual symptoms and functional impairment.

Conceptual Model of ADHD in Adulthood

A conceptual basis for cognitive-behavioral therapy (CBT) in patients with ADHD who are experiencing residual symptoms is illustrated in Figure 1.[2] Dr. Safren stated that the core impairments induce other behavioral deficits, which can result in a perpetual cycle. Specific symptoms such as distractibility, disorganization, difficulty following through on tasks, and impulsivity make the acquisition of effective coping skills challenging for patients with ADHD, unless they receive proper therapy. CBT can interrupt this cycle of symptoms and assist patients in the development and practice of compensatory strategies.

Uncontrolled Trials of Psychosocial Treatments

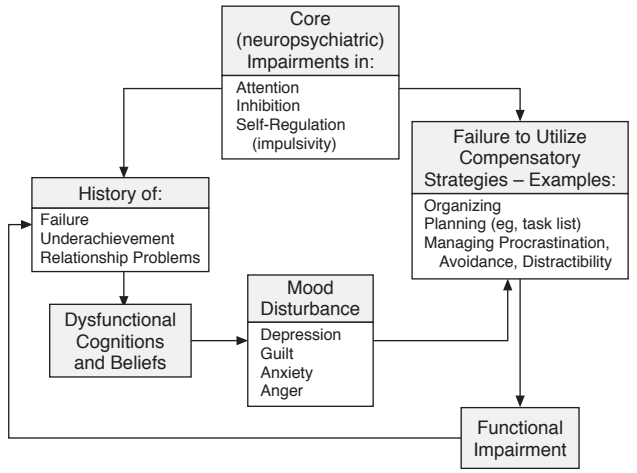
Two uncontrolled trials[3,4] on the evaluation of psychosocial treatments for patients with ADHD showed that CBT can improve ADHD symptoms. The first study[3] used a modified version of Beck's Cognitive Therapy, which included psychoeducation, strategies to change underlying core beliefs, and ways to restructure one's environment. Chart review classification of responders indicated that 69% of participants were "very much improved," and the self-report measures showed improvements in core ADHD symptoms, associated anxiety and depressive symptoms, and global functioning.

In the second study,[4] researchers concluded that ADHD and borderline personality disorder overlap in symptoms. Therefore, they adapted a form of Dialectical Behavioral Therapy, a CBT developed specifically for borderline personality disorder, that included education on ADHD and depression, substance abuse, impulse control, stress, and self-respect and also focused on organization and management strategies, behavior analysis, and emotion exercises. The treatment group showed improvements in ADHD symptoms, depression, and other measures of psychopathology and impairment.

Randomized Trials of Psychosocial Treatments

An Australian research group examined psychosocial treatment, both therapist-delivered and self-directed treatment, for individuals with ADHD.[5,6] The therapist-delivered treatment was a cognitive remediation program to teach ADHD coping strategies incorporating homework exercises, a manual, and a participant workbook. Participants were also

Figure 1. A Cognitive Behavioral Model of Impairment in Adult ADHD



[a]Reprinted with permission from Safren et al.[2]

required to involve a sponsor to help in the overall treatment process. Of the 43 participants, 22 patients self-reported reduced ADHD symptoms, better organizational skills, and reduced anger problems; these gains were still maintained at the 1-year follow-up.

Another study[6] of CBT adapted for minimal therapist contact used a self-help book that emphasized ADHD education, coping strategies, listening skills, organizational skills, and cognitive strategies for anger management and self-esteem. These patients also had a sponsor. At the 2-month follow-up, the treatment group self-reported improved ADHD symptoms, better organizational skills, higher self-esteem, and less anger than the control group.

A Randomized Study of CBT

Dr. Safren's group began to develop a cognitive-behavioral treatment for adult ADHD by interviewing 11 individuals with ADHD who did not achieve full response when treated with pharmacotherapy.[7] The patients reported problems with organizing and planning tasks, distractibility, adaptive thinking, procrastination, anger management, and communication skills. Core and optional treatment modules were created for each of these 6 impairments; however, the modules on communication and anger management were dropped, while a module that includes a spouse or significant other was added in order to facilitate treatment outside of the clinical setting.[9] The research team then completed a preliminary efficacy study comparing patients who received these modules plus continued psychopharmacotherapy to patients who received continued psychopharmacotherapy alone.

CBT in addition to pharmacotherapy was more effective than pharmacotherapy alone. Additionally, those patients who received CBT plus pharmacotherapy had lower independent assessor–rated and self-reported symptoms of ADHD, anxiety, and depression than those patients who received pharmacotherapy alone. Dr. Safren reported that a full-scale efficacy study is currently underway.

Conclusion

Although ADHD is a neurobiological disorder, emerging evidence suggests that skills-building approaches can be advantageous for adults with this chronic and impairing disorder. Psychotherapeutic approaches are new to the treatment of ADHD, but the few studies conducted on this treatment show that skills-based psychotherapy, such as the one designed by Dr. Safren's team,[8,9] can be beneficial as a supplement to medication.

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Primary Care Treatment of ADHD

Larry Culpepper, M.D., M.P.H., began with an overview of ADHD by stating that this disease impairs attention, alertness, vigilance, abstract reasoning, mental flexibility, planning, and working memory. Although there are various presentations of this illness in primary care settings, appropriate evaluation and management strategies can prove to be effective.

Presentation of ADHD

Early childhood diagnosis of ADHD has typically focused on boys, but

according to recent research,[1] there is no association of the child's gender with ADHD and cognitive, psychosocial, school, or family functioning. Symptoms of ADHD in early childhood include hyperactivity, usually accompanied by impulsivity, and inattention. The hyperactive-impulsive subtype of ADHD becomes evident by the age of 4, intensifies over the next 3 to 4 years, and peaks by age 7 or 8 years,[2] whereas the inattentive subtype of ADHD emerges around ages 8 or 9 years. ADHD in children is a diagnosable disorder into young adulthood in 60% to 70% of cases.[3]

Adolescent ADHD is more difficult to diagnose and is characterized by decreased hyperactivity, comorbid disorder development, and a myriad of symptoms ranging from poor school performance to antisocial behavior (Table 2).[4] Adolescents with the inattentive subtype of ADHD are less disruptive and have greater social impairment and unhappiness than those with the hyperactive subtype. Prefrontal and striatal abnormalities are consistent with this behavior in adolescents with a history of ADHD.[5]

Adult ADHD is a true disorder that can be reliably diagnosed and can predict future function and impairment.[6] Adults with ADHD often exhibit poor self-regulation,[7] difficulty prioritizing, disorganization, and restlessness. They may compensate for these impairments through their choices of jobs and living circumstances but will still display impaired social interactions, resulting in a painfully diminished quality of life.

Table 2. ADHD Symptomatology in Adolescents[a]

Alcohol abuse	Ineffective self-monitoring
Antisocial behavior	Lack of task completion
Cognitive fatigue	Legal difficulties
Drug abuse	Loss of motivation
Failing or dropping out of school	Low self-esteem
Impulsivity	Motor vehicle and other accidents
Inattention to detail	Risk taking
Inconsistent performance	Social failure

[a]Data from Wolraich et al.[4]

Evaluation of ADHD

Dr. Culpepper asserted that appropriate evaluations of patients with ADHD include assessing and intervening in critical situations, consulting diagnostic resources, understanding the patient's past management strategies, and testing for medical comorbidities. Due to overlapping symptomatology of other disorders with ADHD, physicians should also interview parents, teachers, coworkers, or spouses to correctly identify and treat ADHD and other comorbidities. Patients with the inattentive subtype of ADHD are more likely to develop comorbid mood and anxiety disorders as well as learning problems, whereas those with hyperactive-impulsive ADHD are more likely to have conduct, oppositional defiant, or substance use disorders.

Management of ADHD

For most patients, pharmacotherapy has beneficial effects on attention, hyperactivity, and impulsiveness and on social and classroom behaviors. Studies of medication treatment in children with ADHD have shown that the agents that are most effective target dopamine and/or norepinephrine receptors.[8,9] Stimulants taken orally, such as methylphenidate, dextroamphetamine, and the combination of amphetamine and dextroamphetamine, are considered first-line treatment for ADHD. One of the difficulties of treating children with oral medication has been dosing during school or extracurricular activities. Trials[10,11] of a methylphenidate patch that uses transdermal technology to deliver continuous medication release throughout the day have been positive and may help to alleviate dosing challenges. The methylphenidate transdermal system was recently approved by the FDA.

Although stimulants have been proven safe and effective for the treatment of ADHD, an estimated 30% to 50% of all children and adults with ADHD either do not respond to or do not tolerate treatment with stimulants.[12] This has led to considerable interest in developing effective, nonstimulant options for treating ADHD. Atomoxetine, tricyclic antidepressants, particularly desipramine and imipramine, and bupropion are among the nonstimulants in use or under review for use in ADHD. In fact, atomoxetine recently became the only nonstimulant medication approved by the FDA for the treatment of ADHD in children, adolescents, and adults. Atomoxetine inhibits the presynaptic norepinephrine transporter, which is believed to improve efficiency in the norepinephrine system and is associated with improved ADHD symptoms.[13]

Two agents that are being reviewed for their effectiveness in ADHD are the antihypertensive guanfacine[14] and the wake-promoting agent modafinil.[15,16] Guanfacine has come under investigation for its use in patients with ADHD who are vulnerable to the abuse liability of stimulants. An α_2-adrenergic agonist, guanfacine may work in ADHD by affecting norepinephrine discharge rates in the locus ceruleus, and this action may indirectly affect dopamine firing rates.[14] Recent studies[15,16] of a new formulation of modafinil, a film-coated tablet administered once daily to children and adolescents with ADHD, have shown improvements in the full spectrum of symptoms of ADHD. Since modafinil has been approved by the FDA to improve wakefulness in patients with excessive sleepiness, researchers theorize that these alerting effects may help to improve attention in children with ADHD. The pharmacologic profile and structure of modafinil is notably different from the stimulants, and there is no demonstrated abuse potential. Modafinil appears to selectively activate the cortex without generalized

effects on the central nervous system. Modafinil film-coated tablets may provide a novel therapeutic option for the management of ADHD in pediatric and adolescent patients.

In addition to pharmacotherapy, Dr. Culpepper recommended behavior therapy for children and adolescents to improve environment management strategies[17] and cognitive behavior therapy or other psychotherapies for adolescents and adults who have long-standing dysfunctional behaviors.

Conclusion

Given the high prevalence, long-term course, and pervasive effects of ADHD on patients and their families, primary care physicians will encounter a variety of presentations of this disorder. ADHD management must be multimodal, with patients benefiting from caring professionals who have expertise in the treatment of ADHD as well as the primary care physician. A long-term therapeutic alliance with the primary care physician will prove to be invaluable to patients and their families in improving their quality of life.

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Drug names: amphetamine/dextroamphetamine (Adderall), atomoxetine (Strattera), bupropion (Wellbutrin and others), clonidine (Catapres and others), desipramine (Norpramin and others), guanfacine (Tenex and others), imipramine (Tofranil and others), methylphenidate (Ritalin, Methylin, and others), modafinil (Provigil), nortriptyline (Pamelor, Aventyl, and others), protriptyline (Vivactil).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, bupropion, clonidine, guanfacine, and modafinil are not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder; methylphenidate is not approved for the treatment of narcolepsy or augmentation for depression; and yohimbine is not approved for the treatment of sexual dysfunction. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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