New Developments in the Treatment of ADHD

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights from a planning teleconference entitled "New Developments in the Treatment of Attention-Deficit/Hyperactivity Disorder," which was held May 16, 2005. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc. and was supported by an educational grant from Cephalon.*

The planning teleconference was chaired by ***Joseph Biederman****, M.D., Chief, Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Department of Psychiatry, Massachusetts General Hospital and 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 Department of Psychiatry, SUNY Upstate Medical University, Syracuse, N.Y.;* ***Alysa E. Doyle****, Ph.D., Director of Neuropsychology, Clinical and Research Programs in Pediatric Psychopharmacology, Massachusetts General Hospital and Harvard Medical School, Boston;* ***Thomas J. Spencer****, M.D., Associate Chief, Clinical and Research Programs in Pediatric Psychopharmacology, Massachusetts General Hospital and Harvard Medical School, Boston;* ***Timothy E. Wilens****, M.D., Clinical and Research Programs in Pediatric Psychopharmacology, Massachusetts General Hospital and Harvard Medical School, Boston;* ***Margaret D. Weiss****, M.D., Ph.D., Department of Psychiatry, University of British Columbia, Vancouver, Canada;* ***Steven A. Safren****, Ph.D., Massachusetts General Hospital and Harvard Medical School, Boston; and* ***Larry Culpepper****, M.D., M.P.H., Department of Family Medicine, Boston University, Boston, Mass.*

Financial disclosure appears at the end of this article.

Introducing the topic, Joseph Biederman, M.D., explained that new developments in the treatment of attention-deficit/hyperactivity disorder (ADHD) include more than useful medications. New developments relate to recent neurobiological research findings, research on comorbid diagnoses, explanations of drug mechanisms of action, nonpharmacologic treatment recommendations, and the role that primary care physicians play in treatment of the disorder.

Fundamentals of ADHD: Circuits and Pathways

Amy F. T. Arnsten, Ph.D., explained that ADHD is highly associated with volumetric differences in the prefrontal cortex (PFC), cerebellum, and possibly striatum. Understanding the neural basis of ADHD aids in understanding how treatments will work, if genetic changes in catecholamine pathways could result in ADHD symptomatology, and if changes in catecholamine actions may result in improvement of the disorder.

The Higher Association Cortices

Dr. Arnsten described the association between the cerebral cortices and ADHD symptomatology (Table 1). Cortical areas are intricately interconnected to provide a unified attentional experience. The higher order sensory cortices process sensory features and can focus on a particular detail. The inferior temporal cortex processes visual features based on color and shape, but repeated experience with the same visual stimulus leads to decreased response,[1] which Dr. Arnsten believed may account for the boredom of repetition such as that found in a school setting.

The posterior parietal cortex plays a critical role in conscious attention by analyzing movement, spatial relationships, and quantity and is important in constructing spatial maps and orienting attention in time and space. The processing of visual stimuli can be diminished by interference from nearby stimuli from the same visual field or by lesions to the right posterior parietal association cortex.

The PFC regulates attention, inhibits the processing of irrelevant stimuli, sustains attention over long delays, and divides and coordinates attention. The PFC has particular relevance to ADHD, as imaging studies indicate that ADHD patients often have smaller PFC volume, particularly on the right side.[2,3] Dr. Arnsten also noted that the PFC uses representational knowledge (working memory) to guide movement and attention, which inhibits inappropriate behavior and controls the processing of irrelevant stimuli. Lesions on the PFC are associated with ADHD symptomatology such as distractibility, poor concentration and organization, impulsivity, and reduced ability to gate sensory input.[4]

Basal Ganglia and Cerebellum

Dr. Arnsten explained that while basal ganglia and the cerebellum have been known to be important for the regulation of movement, their role in higher cognitive function is not fully understood. She related her opinion that basal ganglia and the cerebellum may influence cognition in a manner similar to their influences on movement—the basal ganglia, which are modulated by dopamine, may be important for the planning, selection, initiation, and execution of thoughts, while the cerebellum, which is stimulated by norepinephrine, may improve cognitive function on a faster timescale.

Dopamine. Dr. Arnsten described the action of dopamine D_1, D_2, and D_4

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Table 1. Cortices and Their Relationship With ADHD-Related Impairments

Cortex	Actions	Impairments
Inferior temporal cortex	Processes visual features based on color and shape	Agnosia, difficulty recognizing objects and faces[1]
Posterior parietal cortex	Plays a critical role in conscious attention by analyzing movement, spatial relationships, and quantity	Contralateral neglect, inability to allocate attentional resources to a point in space or time
Prefrontal cortex (PFC)	Regulates attention, inhibits the processing of irrelevant stimuli, sustains attention over long delays, and divides and coordinates attention	Imaging studies indicate that ADHD patients often have smaller PFC volume and lesions on the PFC are associated with ADHD symptomatology[2,3]

receptors (Table 2). D_1 receptor stimulation produces an inverted U dose-response whereby optimal doses improve working memory while high doses impair these functions.[5] Recent electrophysiologic research[6] has shown that D_2 receptor stimulation increases the response-related firing of PFC neurons in monkeys performing a working memory task. D_4 receptors appear to inhibit γ-aminobutyric acid (GABA) transmission, but the actions of these receptors are unclear. Stimulant medication may increase endogenous stimulation of D_4 receptors, which are weakened by ADHD.

Norepinephrine. Dr. Arnsten explained that norepinephrine acts at α_1, α_2, β_1, β_2, and β_3 adrenoceptors and improves PFC function through its actions at postsynaptic α_2 adrenoceptors (see Table 2). The α_{2A} agonist, guanfacine, improves working memory, attention regulation, behavioral inhibition, and/or planning in humans.[7] Research[8] has shown that α_2 receptor stimulation increases delay-related firing. Blocking α_2 receptors in the PFC with yohimbine markedly reduces delay-related cell firing, which acts as the cellular measure of working memory and behavioral inhibition. In addition, blocking α_2 receptors impairs working memory and impulse control and increases hyperactivity. In contrast with α_2 receptor mechanisms, high levels of norepinephrine release, during stress for example, impair PFC function through actions at α_1 receptors coupled to protein kinase C intracellular signaling. Thus, agonists such as phenylephrine impair working memory. Conversely, α_1 antagonists such as urapidil and prazosin protect PFC cognitive abilities, preventing stress-induced PFC impairment. Finally, research[9] on β adrenoceptor actions suggests that stimulation of β_1 adrenoceptors impairs PFC function.

Table 2. Actions of Dopamine and Norepinephrine

Dopamine
Optimal levels of D_1 receptor stimulation reduce noise and improve working memory[5]
D_2 receptor stimulation increases the response-related firing of PFC neurons[6]
D_4 receptors appear to inhibit GABA transmission
Norepinephrine
Acts at α_1, α_2, β_1, β_2, and β_3 adrenoceptors. It improves prefrontal cortical function through stimulation of postsynaptic α_{2A} adrenoceptors
The α_{2A} agonist, guanfacine, improves working memory, attention regulation, behavioral inhibition, and/or planning[7]
Blocking α_2 receptors in the PFC with yohimbine markedly reduces delay-related cell firing and impairs prefrontal cortical function

Abbreviations: GABA = γ-aminobutyric acid, PFC = prefrontal cortex.

Conclusion

Dr. Arnsten concluded by explaining that the PFC appears to thrive under conditions of moderate catecholamine release. Conversely, memory functions are impaired under conditions of high catecholamine release. Catecholamines may, therefore, act as a chemical switch, turning on PFC during normal waking time and turning it off during drowsiness or stress. Medications that optimize catecholamine transmission may normalize the function of these circuits and ameliorate ADHD symptomatology.

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Candidate Gene Studies

Stephen V. Faraone, Ph.D., stated that the development of ADHD may be attributed to both genetic and nongenetic factors. Candidate gene studies of ADHD have produced substantial evidence implicating several genes in the etiology of the disorder. Seven of the 8 genes for which the same variant has been studied in 3 or more case-control or family-based studies have shown statistically significant evidence of an association with ADHD on the basis of pooled odds ratio data (Table 3).[1,2]

Table 3. Significant Pooled Odds Ratios for Gene Variants in 3 or More Case-Control or Family-Based Studies[a]

Gene	Study Design	Pooled OR	95% CI
Dopamine D_4 receptor (exon III VNTR, 7-repeat)	Family	1.16	1.03 to 1.31
Dopamine D_4 receptor (exon III VNTR, 7-repeat)	Case-control	1.45	1.27 to 1.65
Dopamine D_5 receptor (CA repeat, 148 bp)	Family	1.24[b]	1.12 to 1.38
Dopamine transporter (VNTR, 10-repeat)	Family	1.13	1.03 to 1.24
Dopamine β-hydroxylase (*Taq* A)	Case-control	1.33	1.11 to 1.59
SNAP25 (*T1065G*)	Family	1.19	1.03 to 1.38
Serotonin transporter (*5-HTTLPR* long)	Case-control	1.31	1.09 to 1.59
HTR1B (*G861C*)	Family	1.44	1.14 to 1.83

[a]Reprinted with permission from Faraone et al.[1]
[b]Data from Lowe et al.[2]
Abbreviations: OR = odds ratio, SNAP-25 = synaptosomal-associated protein 25, VNTR = variable number of tandem repeats.

Molecular genetic studies and pharmacogenetic studies of family, twin, and adoption subjects provide compelling evidence that genes play a strong role in mediating susceptibility to ADHD.[1,3] Dr. Faraone explained that candidate gene studies have used both case-control designs and family-based designs. In case-control studies, allele frequencies between patients with ADHD and non-ADHD controls are compared. Alleles that confer risk for ADHD should be more common among patients with ADHD. In family-based studies, the alleles transmitted by parents to children are compared with those that they do not transmit. If an allele increases the risk for ADHD, that allele should be more common among the transmitted alleles than the nontransmitted alleles. By reviewing data from both design types and quantifying the odds ratio or relative risk for developing ADHD, the magnitude to which the genetic alleles are associated with ADHD can be assessed.

Catecholaminergic Genes

Dr. Faraone explained that ADHD is associated with deficits in the neural circuits connecting the cerebellum and striatal structures to the PFC. ADHD may disrupt these neural circuits, resulting in the typical symptoms of ADHD such as poor attention, impulsivity, and hyperactivity. The most effective treatments for ADHD facilitate catecholaminergic actions in the PFC, which highlights the role that catecholaminergic receptors and genes play in the pathophysiology of the disorder. Most research on the association between catecholaminergic genes and ADHD is sparse and often contradictory. While the dopamine D_4 receptor gene (*DRD4*) has been implicated in the pathophysiology of ADHD,[4] studies of the dopamine D_5 receptor gene (*DRD5*),[5–11] dopamine transporter gene (*DAT*),[12–25] and dopamine β-hydroxylase (*DBH*)[5,6,21,26–28] genes have found inconsistencies. Other candidate catecholaminergic genes that have been studied but appear to lack an association with ADHD include the dopamine receptors (*DRD2* and *DRD3*), tyrosine hydroxylase (*TH*), catechol-*O*-methyltransferase (*COMT*), and monoamine oxidase A (*MAOA*).

The Noradrenergic System

Dr. Faraone noted that studies of 3 adrenergic receptors, the α_{2A}-adrenergic receptor (*ADRA2A*),[29–32] the α_{2C}-adrenergic receptor (*ADRA2C*),[33–35] and the α_{1C}-adrenergic receptor (*ADRA2C*),[33] have had mixed results but overall do not suggest an association with ADHD.[1] Studies[36–38] of the norepinephrine transporter gene (*SLC6A2*) also found no association with ADHD.

The Serotonergic System

As with many of the studies of the noradrenergic system, Dr. Faraone explained that studies of the serotonergic system, which includes the serotonin receptors and transporters as well as tryptophan hydroxylase, have found substantial inconsistencies. Among serotonin receptor studies,[39–41] gene coding for the serotonin *HTR1B* receptor gene suggests an association with ADHD, and further study is warranted. However, evidence is less consistent and largely negative for the HTR2A gene.

The serotonin transporter gene (*5-HTT*) has been widely studied for its associations with psychiatric disorders. However, its association with ADHD is not clear. Case-control studies[42,43] have shown an association between the *5-HTT* gene and ADHD, while family studies have shown inconsistent results.

Tryptophan hydroxylase (TPH), the rate-limiting enzyme involved in the synthesis of serotonin, has been studied to find associations with ADHD. Research[44] has found that *TPH* polymorphisms have been associated with aggression and impulsivity, two hallmark characteristics of ADHD, indicating a need for further study of this gene.

Other Candidate Genes

Other candidate genes that have had mixed results in uncovering their associations with ADHD include acetylcholine receptor (α_4 subunit) genes (*CHRNA4* and *CHRNA7*),[45–47] glutamate receptor genes (*GRIN2A*),[48] and synaptosomal-associated protein 25 (*SNAP25*) gene.[49–52]

Pharmacogenetic Studies

Dr. Faraone noted that gene variants influence medication response and that the efficacy and adverse events of medications can often be determined with the discovery of gene markers. Dr. Faraone explained that the goal of pharmacogenetic studies is to identify genetic patterns that lend insights into the development of therapeutic agents. Because of the polygenic nature of ADHD and the clinical heterogeneity among patients, ADHD may be better understood in the context of medications that either reduce or ameliorate symptoms. Heterogeneity between candidate gene studies demonstrates the complex genetic architecture of ADHD. Therefore, studies that implement designs to lessen heterogeneity and provide adequate statistical power would be more likely to detect small effects and contributory influences found in many genes.

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Conclusion

Future candidate gene studies of ADHD will require design strategies that will provide enough statistical power to detect genetic differences between patients and, therefore, the biological underpinnings of ADHD. Using genetics as a means to understand disease states may guide clinicians to diagnose and choose viable treatment options.

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Executive Functions

Alysa E. Doyle, Ph.D., related that while the diagnosis of ADHD is based on behavioral symptoms, a large research literature has highlighted associated neurocognitive impairments, particularly in the domain of executive functions. She described executive functions as the higher-order cognitive processes that underlie self-regulation and goal-directed behavior such as working memory, response inhibition, set shifting, abstraction, planning, organization, fluency, and certain aspects of attention.[1] Although executive function deficits have been argued to represent the core of ADHD impairment, neuropsychological heterogeneity appears to exist within the disorder.

Neuropsychological Findings

Dr. Doyle explained that individuals with ADHD exhibit poor performance on clinical neuropsychological tests of attention and executive functions.[2] The most well-known theories of ADHD have argued that specific aspects of executive functions represent the "core" or "primary" deficit in the disorder, with inhibitory control[3] and working memory[4] as proposed core deficits. Other deficits associated with the disorder include set shifting, impulsivity, and impairments in planning and organization. However, studies that have examined whether executive function measures can be used to diagnose ADHD have found such neuropsychological measures are poor diagnostic tools due to variability of performance within ADHD samples.[2] While measures reflecting impaired executive function are generally predictive of a diagnosis of ADHD, normal range scores cannot rule out the disorder[5] because some patients with ADHD are able to perform within the normal range on some or all executive function tests.

Table 4. Possible Explanations for Normal Range Performance of Individuals With ADHD on Executive Function Measures

Measures of executive functions may not always capture frontal system impairments
Because tests developed to assess overt brain damage in adults may lack sensitivity to more mild cognitive deficits that occur within the context of development
Because the structure of the testing session may mask impairments in some individuals
Because individuals may recruit non-frontal cognitive resources to help them solve "frontal" tasks
Impairments in executive functions may not be the "core" deficit in ADHD or may be one of several "core" deficits
Other candidate deficits grounded in both theory and research include problems with state regulation and altered reinforcement mechanisms

Factors Associated With Variability

Dr. Doyle explained that while research supports the association between ADHD and deficits in response inhibition, working memory, and other domains of executive function, the data also reflect variability in performance on such measures. Although only limited attention in the research literature has been given to this topic, Dr. Doyle described several possible factors that may be associated with such variability (Table 4). Research[6,7] has shown an association between a family history of ADHD and executive function impairment, which raises the possibility that familial and nonfamilial cases of ADHD differ neuropsychologically. Also, the presence of comorbid disorders may exacerbate or modify the neuropsychological profile of youths with ADHD. Several studies[8–11] have shown that individuals with ADHD and comorbid learning disorders have greater executive function deficits than individuals with ADHD alone. Different patterns of executive function weaknesses might be associated with inattentive and hyperactive/impulsive symptom dimensions within ADHD.[12] Finally, developmental differences may exist among preschoolers, youth, and adults.

Normal Range Performance on Executive Measures

Dr. Doyle also reviewed 2 possible explanations for normal range performance of some ADHD subjects on executive functions measures. First, such measures may not always capture frontal system impairments because they are imperfect indicators of the latent construct of executive functions.[13] Tests developed to assess adults with overt brain injuries may lack the sensitivity to capture mild cognitive impairments. Additionally, the structured testing situation may mask less severe impairments.[14] Moreover, compensatory mechanisms that allow some individuals to use alternative cognitive resources to solve "frontal" system tasks may also mask underlying impairments in frontal systems.[13] Second, executive function deficits may not be the only core or causal deficit underlying ADHD.[15,16] Other potential deficits underlying the behavioral symptoms of ADHD include altered networks underlying reinforcement contingencies[17] and impairments in state regulation.[18]

Conclusion

Dr. Doyle concluded by stating that because of the variability of subject per-

formance and executive function measures, ADHD may be best understood as a neuropsychologically heterogeneous condition. Behavioral genetic data further support the notion that executive function deficits are etiologically linked to ADHD but do not represent the single underlying deficit in the disorder. Therefore, future studies should further document the neuropsychological heterogeneity of the disorder. Practitioners should also move away from using neuropsychological testing as a diagnostic tool for ADHD. Rather, such testing is best used to create a profile of cognitive strengths and weaknesses that can be helpful for school or career planning.

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ADHD and Comorbidity

Thomas J. Spencer, M.D., stated that individuals with ADHD have high rates of comorbid psychiatric and learning disorders (Table 5).[1–11]

Mood Disorders

According to Dr. Spencer, children with ADHD and mood disorder comorbidity usually have chronic depression compared with the more episodic depression in adult ADHD.[1] An unusual feature of childhood depression is the high rate of switch to mania. Unlike the classic adult presentation of mania in which the patient experiences euphoria, elation, grandiosity, and increased energy, mania presents in children and some adults as extreme irritability and explosive mood. Other symptoms may include decreased sleep, overtalkativeness, racing thoughts, increased goal-directed activity (e.g., social, work, school, or sexual), and manifestations of poor judgment such as thrill-seeking behavior. Juvenile mania also has overlapping developmental features of ADHD that make individual diagnoses difficult.

Childhood Anxiety Disorders

Dr. Spencer explained that the symptoms of anxiety disorders and ADHD also tend to overlap. Childhood anxiety disorders are similar to adult anxiety disorders, are very common, and may persist into adulthood. While the DSM-IV only recognizes 2 childhood anxiety disorders (separation anxiety disorder and selective mutism), many adult anxiety syndromes commonly emerge in childhood and adolescence, such as panic disorder with and without agoraphobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, as well as the atypical anxiety disorders termed *anxiety disorders not otherwise specified*.

Oppositional Defiant Disorder and Conduct Disorder

Dr. Spencer differentiated between oppositional defiant disorder and conduct disorder. Oppositional defiant disorder is characterized by a pattern of negativistic, hostile, and defiant behavior while conduct disorder is a more severe disorder of habitual rule-breaking defined by a pattern of aggression, destruction, lying, stealing, or truancy. Comorbid ADHD and oppositional defiant disorder or conduct disorder tend to occur at high rates, and comorbid conduct disorder has a worse illness course.[12] Children with ADHD and comorbid conduct disorder have an earlier age at onset of conduct disorder, are more aggressive, and have more persistent conduct disorder than children with conduct disorder alone.[13]

Cognitive Performance, Learning Disabilities, and Developmental Disorders

Dr. Spencer reported that many studies[2–4] have noted the association between poor school performance and childhood ADHD. Children with ADHD have poorer grades, are more likely to repeat grades or be placed in special classes, and require more tutoring. Research[14] also suggests that children with ADHD perform more poorly on standard measures of intelligence and achievement than children without ADHD. Learning disabilities and

Table 5. Comorbidity of Other Disorders in Children With ADHD

Comorbid Disorder	Outcome
Mood disorders	Children with ADHD and mood disorder comorbidity usually have chronic depression, adults with ADHD usually have episodic depression[1]
	Childhood switch to mania, unlike adult presentations of mania, is associated with extreme irritability and explosive mood
Childhood anxiety disorders	Symptoms of anxiety disorders and ADHD tend to overlap
	Many adult anxiety syndromes commonly emerge in childhood and adolescence
Oppositional defiant disorder	Oppositional defiant disorder is characterized by a pattern of negative, hostile, and defiant behavior
Conduct disorder	Conduct disorder is characterized by habitual rule-breaking defined by a pattern of aggression, destruction, lying, stealing, or truancy
Cognitive performance, learning disabilities, and developmental disorders	Children with ADHD have poorer grades, are more likely to be placed in special classes or repeat grades, and require more tutoring[2–4]
Tic disorders	Tic disorders appear to have little impact on the severity or chronicity of childhood ADHD[5,6]
Substance use disorders	Juveniles with ADHD are at increased risk for cigarette smoking[7–9] and substance abuse[10,11] during adolescence

ADHD appear to be etiologically independent but co-occur due to nonrandom mating in which individuals with one condition (such as ADHD) chose individuals with another condition (such as learning disabilities) more often than should occur by chance.[2] Children with pervasive developmental disorders (i.e., autism and autistic-like disorders) and the specific developmental disorders (i.e., learning disabilities) often also have psychiatric disorders and behavioral problems.

Tic Disorders

Dr. Spencer noted that tic disorders did not appear to have much of an impact on the severity or chronicity of childhood ADHD. Some studies[5,6] have reported limited consequences and little impact of tics on the course of ADHD. In addition, ADHD and tic disorders appear to be independent in course. Tic disorders have little impact on the rates of other comorbid disorders and indices of psychosocial function in multiple domains (e.g., school, cognitive, social, and family).

Substance Use Disorders

Dr. Spencer explained that studies indicate that juveniles with ADHD are at increased risk for cigarette smoking[7–9] and substance abuse[10,11] during adolescence. Youths with ADHD disproportionately use cigarettes, alcohol, and then drugs, becoming addicted to cigarette smoking at twice the rate of non-ADHD individuals. Youths with ADHD and associated substance abuse tend to prefer the same substances (alcohol and marijuana) as youths without ADHD. Individuals with ADHD, independent of comorbidity, tend to maintain their addiction longer compared with individuals without ADHD.[11]

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Mechanism of Action of Agents Used to Treat ADHD

According to Timothy E. Wilens, M.D., ADHD is largely associated with the dysregulation of dopaminergic and noradrenergic systems in the brainstem, striatum, cerebellum, and front-cortical regions. He also explained that multisite studies[1] highlight the fundamental importance of medications in the management of ADHD.

Medications Used to Treat ADHD

The medications that are most commonly used for the treatment of ADHD include stimulants (methylphenidate and amphetamine), nonstimulants

(atomoxetine), α agonists (clonidine and guanfacine), bupropion, tricyclic antidepressants, and, more recently, agents such as modafinil and nicotinic agonists. Each of these medications has a different mechanism of action (Table 6).

Table 6. Mechanisms of Action in Medications Used to Treat ADHD

Medication	Mechanisms of Action
Stimulants	Blocks the reuptake of dopamine and norepinephrine by increasing synaptic dopamine
Atomoxetine	Inhibits presynaptic norepinephrine reuptake
Clonidine and guanfacine	Modulates presynaptic and postsynaptic norepinephrine
Bupropion	Appears to involve reuptake inhibition of dopamine and norepinephrine, and potentiating dopaminergic neurotransmission
Tricyclic antidepressants	Affects histaminergic and cholinergic receptors, norepinephrine catecholamine reuptake leads to ADHD but efficacy
Modafinil	Appears to affect catecholaminergic neurotransmission—the dopaminergic and noradrenergic systems, in particular
Nicotinic agonists	Reverses nicotinic cholinergic dysregulation

Stimulants. Dr. Wilens explained that preclinical and clinical studies[2–4] have shown that stimulants block the presynaptic reuptake of dopamine and norepinephrine by increasing synaptic dopamine and norepinephrine (although less is known about that system). Whereas methylphenidate and amphetamine both appear to block catecholamine reuptake proteins (resulting in intrasynaptic catecholamine increases), amphetamine also facilitates catecholamine release from presynaptic terminals.

Research[5] has shown that genetic manipulation that results in the elimination ("knockout") of the dopamine transporter protein can lead to behavioral and pharmacological insensitivity to methylphenidate in mice. Other research[6] indicated that noradrenergic effects of stimulants are important therapeutic mechanisms for enhancing functions such as response, working memory, and attention.

Atomoxetine. Dr. Wilens described atomoxetine, a nonstimulant agent approved by the U.S. Food and Drug Administration (FDA) approved for treatment of ADHD in children, adolescents, and adults with ADHD. He explained that atomoxetine inhibits presynaptic norepinephrine reuptake, which results in increased synaptic norepinephrine. Atomoxetine exhibits little effect on serotonin reuptake and has minimal affinity for other receptors, neurotransmitters, or transporters. Researchers speculate[7] that atomoxetine influences the posterior attentional systems that analyze data and response preparation because of its effects on norepinephrine,[8] and increases dopamine levels in the prefrontal cortex, which may be associated with improved executive and other cognitive functioning.

Clonidine and guanfacine. Dr. Wilens noted that the α agonists clonidine and guanfacine share important features that modulate both presynaptic and postsynaptic norepinephrine. Clonidine is an antihypertensive medication with α-adrenergic agonist properties that has been shown to be effective in treating ADHD and tics.[9] It appears to block the release of norepinephrine from central catecholaminergic nerve terminals. Clonidine can also interact with other neurotransmitter systems such as catecholamines, indolamines, cholinergic, opioidergic, and amino acid systems. Guanfacine, also effective in ADHD with tics,[10] parallels the effects of clonidine and is an effective agonist of the α_{2A} receptor and, as such, mimics norepinephrine at α_{2A} receptors.

Bupropion. Dr. Wilens next described bupropion, a novel aminoketone antidepressant that is related to the phenylisopropylamines and is pharmacologically distinct from available antidepressants. The mechanism of action of bupropion appears to involve reuptake inhibition of dopamine and norepinephrine and potentiation of dopaminergic neurotransmission.[11]

Tricyclic antidepressants. Tricyclic antidepressants, according to Dr. Wilens, have been shown to be efficacious in studies of children and adults with ADHD. Although tricyclic antidepressants affect histaminergic and cholinergic receptors, research[12] indicates that they are effective in treating ADHD because of their effect on catecholamine reuptake, particularly that of norepinephrine. Tricyclic antidepressants have redundancy of activity with stimulants.

Modafinil. Dr. Wilens related that modafinil is a very recently FDA approved nonstimulant medication used in the treatment of narcolepsy, but that treatment with modafinil for ADHD has been found to be effective in treating children with ADHD.[13,14] Despite the finding of efficacy, the precise mechanism or areas of action of modafinil in relation to the treatment of ADHD is not fully understood. Modafinil seems to exert effects on the hypothalamus and attenuates both cholinergic and monoaminergic components of the ascending reticular activating system. Modafinil affects the ventrolateral preoptic nucleus (downstreaming affecting the locus ceruleus site of noradrenergic cell bodies) and the tuberomammillary nucleus (histamine neurons). Modafinil also appears to have marginal effects on catecholaminergic neurotransmission, in particular, dopaminergic and noradrenergic systems,[13] that may in part describe its efficacy in ADHD.

Nicotinic agonists. Dr. Wilens explained that ADHD has been shown to be associated with an increased risk and earlier age at onset of nicotine use and cigarette smoking than in non-ADHD controls[15] and that maternal smoking during pregnancy increases the risk for ADHD in the offspring.[16] Treatments that incorporate nicotinic properties may improve ADHD.[17]

Conclusion

Dr. Wilens concluded by highlighting the common mechanisms of action of the various agents used in ADHD, such as the attenuation of central cate-

cholaminergic neurotransmission. Understanding the various mechanisms of action of ADHD medications will undoubtedly help in the future pharmacology of ADHD. He noted that because of pharmacogenomic relationships in ADHD, practitioners may choose agents based on matching the patient's genotype with the diverse physiological mechanisms of action of the various medications for ADHD.

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Effectiveness Outcomes

Margaret D. Weiss, M.D., Ph.D., opened her discussion of treatment methodology of ADHD by describing the difference between efficacy studies, which demonstrate the potential of a treatment to impact the symptoms of a disorder, and effectiveness studies, which show whether or not treatments actually work in practice.[1] The outcome of treatment on patients in the clinical setting may be quite different from outcomes seen in the controlled environment of a research protocol. Physicians need to be cautious in generalizing study results from short-term studies in compliant patients with a primary diagnosis of ADHD to settings in which patients have multiple social and psychiatric problems, are treated with multiple medications with modest compliance, and receive intermittent follow-up care.

Problems With Studies

Dr. Weiss explained that more than three quarters of patients in clinical settings will have one or more clinically significant disorders.[2,3] Patients who require treatment for a comorbid condition are excluded from most efficacy studies. Unlike the conditions found in efficacy studies, which are short term and in which noncompliant patients are discontinued, patients seen in practice have considerable difficulty complying with treatment over the long term. Although in an intent-to-treat analysis the ratings of the last visit are carried forward as an end point, the ratings may have been obtained while the patients were still in the study and on medication. This method of preserving data does not reflect how the patient is doing off medication at the point in time when the study is complete. Patients in practice have other problems that can complicate treatment, such as difficult families, problems with language and immigration, medical conditions, and lack of adequate resources for follow-up.

The process of selecting consenting patients for research studies is also biased in that most studies demand families who are motivated, English speaking, able to get to the appointment, and sophisticated enough to understand potential risks. The intervention of just being in a protocol is rarely studied as a therapy in its own right. However, providing the structure, education, rating scales, and systematic evaluation that are routine in efficacy studies may in itself impact on the patient's insight and response. To assume that the placebo group controls for all these "nonspecific" factors is problematic because this has not been shown to be the case in practice. Clinical realities require a threshold of expertise and care for a substantive percentage of patients on either placebo or medication to get better, and if that care is not provided, even active treatment with medication can fail to differentiate from placebo. One of the lessons learned in the Multimodal Treatment Study of Children with ADHD, for example, was that medications used in practice may act quite differently than medication as used in a trial setting.

If physicians need to exercise caution when applying generalized efficacy studies to the realities of the clinical setting, then we also need to look at the clinical realities of the individual

patient when using treatment algorithms, which are generated from efficacy studies and may be more or less relevant to individual patients. The level of evidence for ADHD treatment may be marginal, and the major factor in choosing one or another treatment may be based on only one outcome such as the effect size on core symptoms. Algorithms work from the assumption that all other factors—such as problems with sleep, health, anxiety, mood, learning, tics, and compliance—are equal. When patients seen in practice present with other clinical concerns, these concerns may complicate treatment and may become a primary determinant of outcome in their own right. Novel research designs (e.g., the practical clinical trial) have been developed that modify the typical randomized clinical trial to include naturalistic conditions such as minimizing exclusion criteria, permitting flexible treatment regimens, and measuring rather than forcing compliance.[4]

Conclusion

Dr. Weiss concluded by describing the differences in perception between patients and clinicians—patients want clinicians to treat the illness they have while clinicians want patients to have the illness they treat. In other words, clinicians often focus on the disorder rather than a patient's desire to be able to function better. Effectiveness studies have the potential to let clinicians know how well treatments meet that patient expectation.

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Cognitive Behavioral Approaches to ADHD Treatment in Adults

Steven A. Safren, Ph.D., opened by emphasizing the importance of psychopharmacology in the treatment of ADHD. However, he stated that while psychopharmacology can lessen some of the core symptoms of ADHD (i.e., attentional problems, high activity, and impulsivity), it does not give patients concrete strategies and skills for coping with the impairments associated with ADHD.[1,2] The addition of psychosocial treatment to enhance the effect of psychopharmacologic interventions can help prevent an exacerbation of symptoms due to poor patient coping skills.[1,3–5] However, few studies have evaluated the efficacy of psychosocial interventions for adults with ADHD despite the fact that adults may be more suited for psychosocial interventions than children because adults may be better motivated to adhere to treatment recommendations.

ADHD and Coping Skills

Dr. Safren explained that specific symptoms of ADHD, such as distractibility, disorganization, and difficulty completing tasks, prevent patients from acquiring life skills.[6,7] Patients may exacerbate their symptoms by falling into a cycle of reinforcing negative cognitions and beliefs because of failures and underachievement, especially adult patients who have been suffering from ADHD since childhood and may have a long history of failures and underachievement. Cognitive behavioral treatments, such as behavioral skills training, following treatment with medications may interrupt the continuous cycle of symptoms. Patients develop and practice effective compensatory strategies including organizing, planning, and avoidance management, which help to disrupt the link between core symptoms and failures and underachievement.

Uncontrolled Studies of Psychosocial Treatments

Despite the lack of research investigating the efficacy of psychosocial treatments for ADHD, Dr. Safren noted that the few evaluations[8–11] available have yielded encouraging results that suggest psychosocial treatment can lead to a beneficial patient outcome. In one study,[8] patients were trained to control dysfunctional cognitions by treating their thoughts as hypotheses rather than facts. Patients were trained to look for negative biases and to reevaluate their thoughts. Results based on self-report measures showed that 69% of patients reported that their condition was "much improved" or "very much improved." A study from Germany[9] investigated the efficacy of treating adult ADHD with dialectical behavioral therapy, a cognitive-behavioral treatment developed for borderline personality disorder, because ADHD and borderline personality disorder share overlapping symptoms. The treatment group improved more than the control group. In addition, Australian researchers looked into the benefits of therapist-delivered[10] and self-directed[11] psychosocial treatment for adults with ADHD. The therapist trial[10] showed that many of the gains were maintained at 1-year follow-up. The self-directed treatment[11] also led to improvement that was maintained at 2 months' follow-up.

Randomized Study of Cognitive-Behavioral Therapy (CBT)

Dr. Safren next described a randomized study[12] of cognitive-behavioral therapy (CBT) conducted by his own research group that found CBT was superior to continued medications alone. The treatment was broken into 6 modules to address specific facets of the patient's ADHD. The core set of 3 modules addressed issues applicable to all adult patients with ADHD: organizing and planning, distractibility, and cognitive restructuring (adaptive thinking). The optional set of 3, available based on patient need, focused on procrastination, anger and frustration management, and communication skills. Evaluation of the study was made by self-report measures

and an independent evaluation made by an assessor who was blind to treatment assignment. At the outcome assessment, patients who were randomized to CBT had lower assessor and self-reported ADHD symptoms ratings than those randomized to continued psychopharmacology alone. Those in the CBT group also had lower assessor-rated and self-reported anxiety, lower assessor-rated depression, and a trend to have lower self-reported depression. The results suggest the superiority of CBT over continued psychopharmacology alone.

Conclusions

Dr. Safren stated that empirical investigations of psychotherapeutic approaches are just beginning despite the fact that published guidelines suggest treating ADHD with a combination of psychotherapy with medications. Available studies show that the addition of skills-based psychotherapeutic approaches as a supplement to medications can lead to a more beneficial patient outcome than medication alone. Dr. Safren's research group provide client manuals[13] and a therapist guide[14] for treatment, which are designed as practical treatment guides for symptoms not fully treated by medications alone. Dr. Safren concluded by explaining that even though ADHD is primarily a neurobiological disorder, emerging evidence suggests that a skills-building approach can have beneficial effects for adults.

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The Role of Primary Care Physicians in Treating ADHD

Larry Culpepper, M.D., M.P.H., began by explaining the importance of primary care physicians in evaluating and treating ADHD. Primary care physicians provide care that can positively affect the function and the quality of life of patients with ADHD. Patients often receive psychiatric treatment (such as antidepressant treatment) first from primary care physicians. In addition, management of life-long disorders such as ADHD may take place at the primary care level. Primary care physicians and psychiatrists need to work together in the evaluation and treatment of patients with ADHD.

Evaluating ADHD in Primary Care

Dr. Culpepper related that because ADHD has a strong genetic association,[1] the primary care physician—especially a family physician—may see ADHD symptoms expressed in several members of a single family at different ages. The symptoms may indicate a long-term illness that can last into adulthood[2] and require constant monitoring at the primary care level. Children may exhibit symptoms such as hyperactivity and impulsivity between the ages of 4 and 6 years. Inattention, which may not become apparent until the child is in school, usually manifests by the ages of 8 or 9 years.[3] Between 60% and 70% of childhood cases of ADHD continue into young adulthood.[4] By adulthood, impairments such as neurologic disinhibition and impulsivity are associated with diminished quality of life and social dysfunction.

Dr. Culpepper described the role of primary care physicians as the first-line of recognition and treatment, because patients with concerns that they might have ADHD usually see a primary care physician first. The patient evaluation requires multiple primary care visits that incorporate education about the disorder for both the patient and the patient's family members and assessment of the severity of the disorder and whether or not the patient is in a crisis situation.

Confirming the Diagnosis

For an evaluation of childhood ADHD, primary care physicians should first screen for DSM-IV diagnostic criteria, interviewing informants as needed. Reports of ADHD symptoms from parent or teacher observations, however, can differ and therefore be problematic and unreliable.[5] Parents do not usually see child behavior at school, and teachers do not usually see child behavior at home. Teacher or coach reports can become more reliable as the school year progresses, but only after the teacher becomes more familiar with the child. Adults with suspected ADHD can be diagnosed by looking at the patient's history, especially childhood, and asking an informant such as a parent or spouse in addition to self-report.

Identifying Comorbid Conditions

Several conditions and disorders are prevalent among patients with ADHD. Primary care physicians need to be at-

tentive to the kinds of comorbidities patients with ADHD have. In addition to oppositional defiant disorder, conduct disorder, substance abuse, anxiety, mood disorders, and learning disabilities described by Dr. Spencer elsewhere in this Academic Highlights, Dr. Culpepper cited hearing or vision impairment and enuresis as comorbid conditions in children. Comorbidities may become evident through the long-term relationship between a patient's family and the primary care physician. Comorbidities can also be discovered through a thorough patient history and a physical examination.

Developing a Comprehensive Assessment

Dr. Culpepper explained that the primary care evaluation should conclude with a summary of the patient-specific aspects of ADHD, which includes the specific subtype of ADHD that the patient expresses, the presence of any comorbid conditions, and any previous management strategies.[6] Physicians also should take note of the developmental, academic, and social impact that both ADHD and any comorbid conditions might have on the patient so that management of these issues can be factored into the treatment plan. Formulation of the treatment strategy may require consultation with a specialist.

Conclusion

Dr. Culpepper detailed successful management of ADHD as beginning with a therapeutic alliance between the patient and physician(s). Initial care should address any immediate crisis, which should be directed by the primary care physician or through referral. As the crisis stabilizes, effective management strategies should be implemented, including patient and family education about ADHD, the establishment of 3 to 6 goals for the patient to reach, treatment with stimulant medication and other supportive interventions, follow-up, and monitoring.[7] Dr. Culpepper concluded that the role of the primary care physician will change over course of the patient's illness but remains critical to optimizing long-term success. The primary care physician has a major role in assuring preventive care and recognizing and treating acute and chronic comorbid illnesses as they develop over time.

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Drug names: amphetamine (Adderall XR, Dextroamp Saccharate, and others), atomoxetine (Strattera), bupropion (Wellbutrin and others), clonidine (Iopidine, Clorpres, and others), guanfacine (Tenex and others), methylphenidate (Focalin, Ritalin, and others), modafinil (Provigil), prazosin (Minizide and others).

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 as 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.

Faculty financial disclosure: In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME article were asked to complete a statement regarding all relevant financial relationships between themselves or their spouse/partner and any commercial interest (i.e., a proprietary entity producing health care goods or services) occurring within the 12 months prior to joining this activity. The CME Institute has resolved any conflicts of interest that were identified. The disclosures are as follows: **Dr. Biederman** has received research support from Shire, Eli Lilly, Pfizer, McNeil, Abbott, Bristol-Myers Squibb, New River Pharmaceuticals, Cephalon, Janssen, Neurosearch, Stanley Medical Research Institute, Lilly Foundation, Prechter Foundation, National Institute of Mental Health (NIMH), National Institute of Child Health and Human Development (NICHD), and National Institute on Drug Abuse (NIDA); is a member of the speaker's bureaus of Shire, Eli Lilly, McNeil, and Cephalon; and is on the advisory boards of Shire, Eli Lilly, McNeil, Janssen, Novartis, and Cephalon. **Dr. Arnsten** has received grant/research support from and has license agreements with Shire and Marinus, and has received grant support from NIMH, National Institute on Aging (NIA), Stanley Medical Research Institute, and National Alliance for Research on Schizophrenia and Depression. **Dr. Culpepper** is a consultant for and member of the advisory boards of Forest, Pfizer, Wyeth, and Eli Lilly. **Dr. Doyle** is a member of the speaker's bureau of McNeil. **Dr. Faraone** is a consultant for and has been involved in pharmaceutical development for McNeil, Novartis, Shire, and Eli Lilly; has received grant/research support from McNeil, Shire, and Eli Lilly; and is a member of the speaker's or advisory boards of Cephalon, McNeil, and Shire. **Dr. Spencer** has received research support from McNeil, Novartis, Shire, Eli Lilly, Pfizer, Janssen, and NIMH; is a member of the speaker's bureaus of Eli Lilly, Novartis, Shire, and McNeil; and is on the advisory boards of Eli Lilly, Shire, Novartis, McNeil, Janssen, and Johnson & Johnson. **Dr. Weiss** is a consultant for Novartis, Eli Lilly, Shire, Janssen, Circa Dia and Purdue; has received grant/research support from Purdue, Circa Dia, Eli Lilly, Shire, Janssen, Human Early Learning Project, and Canadian Institutes of Health Research; has received honoraria from Novartis, Eli Lilly, Shire, and Janssen; and is a member for the advisory boards of Novartis, Eli Lilly, Shire, and Janssen. **Dr. Wilens** has received grants from, is a member of the speaker's bureaus for, and is a consultant for Abbott, Alza/Ortho-McNeil, Celltech, GlaxoSmithKline, Janssen, Eli Lilly, NIDA, NIMH, Neurosearch, Novartis, Pfizer, Saegis, Sanofi-Synthelabo, and Shire. **Dr. Safren** has no significant commercial relationships to disclose relative to the presentation.

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