ADHD: Applying Practice Guidelines to Improve Patient Outcome and Executive Function

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the planning teleconferences "ADHD: Applying Practice Guidelines to Improve Patient Outcome and Executive Function," which were held in August and September 2006. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from McNeil Pharmaceuticals.*

The planning teleconferences were chaired by ***Joseph Biederman****, M.D., Department of Psychiatry, Harvard Medical School and Department of Pediatric Psychopharmacology, Massachusetts General Hospital, Boston. The faculty were* ***Steven A. Safren****, Ph.D., Department of Psychiatry, Harvard Medical School and Department of Behavioral Medicine, Massachusetts General Hospital, Boston;* ***Larry J. Seidman****, Ph.D., Department of Psychiatry, Harvard Medical School and Department of Pediatric Psychopharmacology, Massachusetts General Hospital, Boston;* ***Thomas J. Spencer****, M.D., Department of Psychiatry, Harvard Medical School and Department of Pediatric Psychopharmacology, Massachusetts General Hospital, Boston; and* ***Timothy E. Wilens****, M.D., Department of Psychiatry, Harvard Medical School and Department of Pediatric Psychopharmacology, Massachusetts General Hospital, Boston.*

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An Overview on Advances in the Neurobiology of ADHD

The neural networks in the brain responsible for attention, cognition, and executive functioning, as indicated by Joseph Biederman, M.D., include the prefrontal cortex (PFC), parietal cortex, cingulate gyrus, cerebellum, basal ganglia, thalamus, brain stem reticular formation, and limbic structures such as the amygdala and the hippocampus. According to Dr. Biederman, disruptions in any of these circuits can produce problems with cognition and executive functioning. The cortices of attention are interconnected with each other as well as with subcortical regions of the brain involved in attention.[1]

Neurobiological Studies of ADHD

Brain imaging studies[2–7] of children with ADHD have shown differences in critical regions of the brain, specifically asymmetry of the caudate nucleus, difference in the size and shape of the corpus collosum, smaller right frontal area, smaller right basal ganglia, and smaller vermis of the cerebellum. Because these studies have generally been small and many participants have been medicated, these studies raise concerns as to whether the findings reflect the disorder or its treatment.

Castellanos et al.[2] conducted a large study of 152 children with ADHD compared with 139 age- and sex-matched controls and found that patients with ADHD had significantly smaller total cerebral and cerebellar volumes independent of medication status. Volumetric differences correlated with clinician- and parent-rated severity levels. The authors concluded that in individuals with ADHD, genetic or early environmental influences are operant in brain development; these are fixed, nonprogressive, and unrelated to stimulant treatment. A recent meta-analysis by Valera et al.[8] showed that key regions of the brain involved with attention and executive functions are significantly smaller in children with ADHD compared with children without ADHD with large effect sizes, indicating that the brains of children with ADHD are very different from the brains of children without ADHD.

In the first magnetic resonance imaging (MRI) study of adults with ADHD, Dr. Biederman stated that he and his colleagues[5] showed smaller volumetric dorsolateral PFC and anterior cingulate regions and larger white matter in the brains of adults with ADHD compared with those without ADHD. A recent MRI study[9] assessing cortical thickness showed the dorsolateral PFC and anterior cingulate regions to be dramatically thinner in adults with ADHD compared with controls.

Dr. Biederman also reported that functional MRI (fMRI) studies of adults with ADHD showed impaired activation of the dorsal anterior cingulate cortex. For example, when presented with the Counting Stroop, a Stroop assessment specialized for fMRI, adults with ADHD did complete the cognitive task, but the anterior cingulate was not activated as in normal controls.[10] Instead, a frontostriatal-insular network was activated in adults with ADHD, signifying that these adults have impaired functioning in the anterior cingulate region of the brain. Dr. Biederman stressed that although

neuroimaging studies establish ADHD as a brain disorder, they are not useful for diagnosing ADHD because so much interpatient variability exists.

Sonuga-Barke[11] recently developed a dual-pathway model combining executive function deficits and reward circuits to explain the underlying neuropsychology of ADHD. In this model, patients with ADHD have difficulty in directed attention—the attention needed to engage the brain in uninteresting tasks—and have inhibitory problems, which demonstrates a disturbance in the executive circuit. Equally important is the role of the fascination circuit, a reward system circuit that promises compensation in time; however, patients with ADHD are impatient, cannot wait to receive the reward, and have delay aversion. Dr. Biederman noted that these 2 neuropsychological impairments have been documented in neuropsychological testing and appear to be present in patients with ADHD.

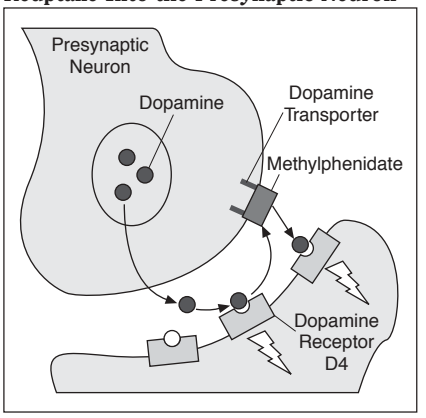
Pathophysiologic Perspective of ADHD

From a pathophysiologic perspective, ADHD is considered to be a disorder of dopamine and norepinephrine dysregulation, largely based on the effects of medicines used to treat ADHD that modify these neurotransmitters.[12] Neurons that produce dopamine and norepinephrine originate in the mesencephalon. The nuclei of the dopaminergic system (the substantia nigra and the anterior tegmentum) and the norepinephrine system (the locus ceruleus) project diffusely to the entire brain. The cortical projections that go to the dorsolateral PFC, anterior cingulate, and ventrolateral PFC are the important circuitry involved in ADHD.

Genetic Perspective of ADHD

From the genetic perspective, Dr. Biederman stated that ADHD has been shown to be a familial disorder; the risk to relatives of family members with ADHD is 5- to 7-fold.[13–15] Twin studies[16–18] support the higher concordance in monozygotic twins compared with dizygotic twins. Based on twin studies, the coefficient for ADHD heritability has been estimated to be approximately 80%.[19] Additionally, adoption studies[16,17] indicate higher rates of ADHD in biological parents as opposed to adoptive relatives. Further, molecular genetic studies[16–18] have consistently identified genes in the dopaminergic and serotonergic families that have been associated with ADHD.

Figure 1. Methylphenidate Blocks the Dopamine Transporter During Reuptake Into the Presynaptic Neuron



Genes that have been associated with ADHD are genes that are involved in the synthesis, metabolization, and release of dopamine. Individual genes in the dopamine family that have been implicated in ADHD include mutations in the dopamine transporter (DAT) gene, as well as mutations in dopamine receptors D_4 and D_5.[20–23] The physiologic implication of this process is to lower the deliverance and dopamine. Stimulants, in general, act therapeutically by blocking the dopamine transporter and augmenting the stimulus (Figure 1).

In individual meta-analyses[19] of ADHD, other genes that have been associated with this disorder include mutations in the serotonin-1B receptor; serotonin transporter; synaptosome-associated protein (SNAP-25), a gene involved in the release of presynaptic dopamine; dopamine β-hydroxylase gene, a gene involved in the conversion of dopamine to norepinephrine; and mutations in the dopamine D_4 and D_5 receptors. These are common genes, and abnormalities in these genes may increase the odds of having ADHD, but they do not directly cause ADHD.

Other Neurobiological Factors to Consider

If ADHD is left untreated, adults with ADHD have a 55% risk of having a lifetime diagnosis of alcohol or drug abuse or dependence.[24] Further, the risk for substance abuse is compounded by the fact that stimulants used to treat ADHD share the same mechanism of action with cocaine—both substances block the reuptake of dopamine into the presynaptic neuron. However, as Volkow and Swanson.[25] demonstrated, while the intravenous administration of both methylphenidate and cocaine produces a euphoric effect, the oral administration of methylphenidate produces a slow uptake into the brain and does not have the reinforcing effects of cocaine. Dr. Biederman and colleagues[24] also found that pharmacotherapeutically treating children with ADHD decreased their risk for developing addiction disorders 3-fold compared with children with untreated ADHD.

According to Dr. Biederman, other challenges for patients with ADHD include increased risk of car accidents, impaired academic performance, problems with employment, substance use disorders, and familial problems. Barkley et al.[26] found that adolescents with ADHD used less sound driving habits and were more likely to have had car accidents, to have had bodily injury as a result of car accidents, and to be at fault for more car accidents than adolescents without ADHD. Concerning academic performance, Biederman and colleagues[27] found that adults with ADHD were more likely to have poor academic histories, need tutoring and placement in special classes, and, of those participants with ADHD, 30% repeated a grade. Several of the adults had employment difficulty, with approximately 50% of the participants being unemployed and another substantial amount being under-

employed. Over a period of 10 years, adults with ADHD had twice as many jobs as control subjects, with almost half of the sample reporting being fired or quitting due to ADHD-related problems. In this sample,[27] untreated adults also had higher rates of cigarette smoking, alcohol use, drug use, and legal problems compared with adults without ADHD. Additionally, ADHD increased the risk of family and social problems. For example, adults with ADHD tended to have a higher risk of divorce or separation, have more difficulties with the family of origin, and have more social difficulties, prompting Dr. Biederman to emphasize that ADHD touches every aspect of life if left untreated.

Conclusion

ADHD is a serious neurobiological disorder with complex etiology and a strong genetic component that frequently affects both adults and children. Dr. Biederman reiterated that ADHD is a familial disorder and that the patterns of comorbidities and deficits are similar across the life cycle. Neuroimaging studies have the capabilities to show the affected regions of the brain, implicating areas for further research into the treatment of ADHD. Dr. Biederman concluded that this illness is impairing in children and adults, and treatment that is efficacious in children can also be effective in adults.

Psychosocial Management of ADHD in Adults, Including the Use of Cognitive-Behavioral Therapy

Steven A. Safren, Ph.D., opened by explaining that cognitive-behavioral therapy (CBT) is a structured, skills-based psychosocial treatment that differs from traditional psychotherapy in several ways. Some of these are that patients agree upon an agenda with the therapist, complete homework outside of therapy sessions, and, consequently, learn life-coping skills. Because the particular CBT techniques vary for different disorders, the particular method of CBT used should be matched to the patient's presenting disorder and individual needs.

Empirical Validity of CBT

Although psychosocial treatments are behavioral and noningestional, there is still the need for a strong evidence base. To rigorously test psychosocial treatments, Dr. Safren, recommended completing the following steps: (1) conceptualize the psychosocial intervention; (2) determine if the treatment is feasible and accepted by patients, usually with a circumscribed sample; (3) delineate manuals and operationalize study materials; (4) estimate the effect on the circumscribed sample to maximize internal validity; and (5) perform tightly controlled efficacy studies, additional efficacy studies, and effectiveness research to validate the generalizability of the psychosocial treatment. These steps are informed by Rounsaville et al.[28] The American Psychological Association has established criteria for empirically supported psychosocial treatments which include the following: (1) randomized, controlled trials must be completed in which the treatment is compared to either no treatment or an alternative therapy, (2) there must be more than 1 study conducted by more than 1 team of scientists, and (3) the treatments need to be documented and replicable.[29]

CBT has been widely studied and empirically supported for anxiety and depression.[30] For example, the implementation of CBT has produced quantifiable symptomatic improvements in patients with anxiety disorders such as panic,[31] social phobia,[32] obsessive-compulsive,[33] generalized anxiety,[34] and posttraumatic stress.[35] Similarly, studies[36–40] on depression reported substantial benefits for patients who received CBT, and several indicated that relapse rates for CBT were comparable to[37] or better than[36] those for pharmacotherapy alone. CBT has been shown to be effective for treating other conditions, including eating disorders,[41,42] trichotillomania,[43] marital distress,[44,45] and sexual dysfunction.[46] Dr. Safren stated that cognitive-behavioral treatments only recently have begun to emerge for the treatment of adults with ADHD.

CBT for Adults With ADHD

The primary treatment for adults with ADHD is pharmacotherapy, which may control symptom severity but does not fully treat the disorder. Approximately 20% to 50% of adult patients with ADHD are considered nonresponders to medication because of insufficient symptom reduction or intolerability.[47–49] Moreover, patients who do respond to pharmacotherapy experience a reduction in only half or fewer of the core symptoms of ADHD.[47,48] Dr. Safren emphasized that CBT can provide adults with concrete coping skills necessary to effectively manage the disorder, which medications cannot provide.

Adults are an ideal treatment population for CBT in ADHD because they are self-referred and therefore may be more motivated than children to adhere to treatment regimens. Also, adults who have ADHD that went undetected and untreated during childhood may have never learned the essential coping skills necessary to thrive in real-world situations, which CBT can supply. Dr. Safren has articulated a model of continued dysfunction in adults with ADHD who show continued symptoms.[50] According to this model, adults with ADHD have core neuropsychiatric impairments that affect attention, inhibition, and self-regulation or impulsivity. Because of these impairments, patients with ADHD are unable to use compensatory strategies such as skills for organizing, planning, and managing procrastination or distractibility, which results in functional impairment. When these impairments continue over time, patients develop a history of failure, underachievement, or relationship problems. With the persistence of cognitive impairments as well, patients may experience negative feelings

Table 1. Cognitive-Behavioral Treatment Modules for Adults With ADHD Delivered Over 12 Weeks[55,56]

Core Modules	Description
Organizing and planning	Introduce patients to the CBT model, dispel myths about ADHD, agree on the structured treatment Begin calendar and task list system Prioritize tasks: Assign an A, B, or C rating to a task Teach problem-solving skills: Select an action plan by listing several different solutions and the pros and cons to each Break overwhelming tasks into manageable steps Teach paper organization
Coping with distractibility	Time patients' attention span Exercise distractibility delay: When patients are distracted, have them write down the distraction and once they are done with that chunk of work, address the distractions If the distractions need more attention, put them on the task list Help patients modify their work area to keep it neat
Cognitive restructuring or adaptive thinking	Present the cognitive-behavioral model of mood where thoughts, feelings, and behaviors are interlinked Perform cognitive restructuring: Teach patients to identify their automatic, negative thoughts about a situation and their mood intensity Assess the errors in these thoughts Restructure their thoughts into a rational response
Optional Modules	
Procrastination	Discuss the attractiveness of procrastination Discuss the negative aspects of procrastination Adapt their problem-solving skills Teach them adaptive-thinking skills Identify areas for home practice
Involvement of a significant or supportive other	Try to do this step at the beginning of treatment Discuss their role as supporters: Remind them to coach and not nag Review the most problematic symptoms of the patient Give them an overview of the treatment

about their situation or themselves. These feelings may lead to mood disturbances and difficulties using compensatory strategies, resulting in a perpetual cycle of impairment and dysfunction. Dr. Safren stated that CBT in combination with pharmacotherapy aims to interrupt that cycle.

Empirical Validity of CBT for Adults With ADHD

An Australian group conducted 2 small studies[51,52] measuring the efficacy of therapist-delivered and self-directed CBT and found significant self-reported improvements in ADHD symptoms and organizational skills. In both studies, a significant or supportive other regularly assisted patients with the treatment programs. Dr. Safren stated that several other studies are in progress to determine the empirical efficacy of CBT in adults with ADHD.

In 2005, Dr. Safren and colleagues[53] conducted a randomized, placebo-controlled trial of 31 adults with ADHD who were stable on medication when they entered the trial. The objective of this study was to examine the difference between CBT plus continued psychopharmacology as prescribed by their provider versus psychopharmacology alone using independent evaluator assessments (ADHD Rating Scale, Hamilton Rating Scales for Depression and Anxiety [HAM-D, HAM-A], and the Clinical Global Impressions-Severity [CGI][54]) and self-report measures (ADHD Current Symptoms Scale, Beck Depression Inventory [BDI], and Beck Anxiety Inventory). In the pretest/posttest analysis, the CBT plus continued psychopharmacology group had lower scores on all assessment measures with significant effect sizes reported for the ADHD Rating Scale (1.2) and for the CGI (1.4). Further, the CBT group also had more treatment responders than the psychopharmacology alone group (56% versus 13%, respectively), with response being conservatively defined as a 2-point reduction on the CGI.

Presently, Dr. Safren stated that he and his colleagues are completing a 5-year efficacy trial comparing CBT (Table 1)[55,56] to progressive muscle relaxation and educational support. In this study, the control group learns relaxation skills and how to apply them to their ADHD symptomatology. A requirement for entry into this study was that patients with ADHD had to be stable on adequate medications for ADHD.

Conclusion

Dr. Safren reiterated that psychosocial treatments have promise as add-on therapeutic methods for treating adults with ADHD. However, studies to date have mostly examined small samples and therefore results are not necessarily generalizable. Larger studies are currently underway to demonstrate the efficacy of psychosocial and cognitive-behavioral treatments for adults with ADHD. A full description of the approach used in Dr. Safren's and colleagues' programs can be found in their therapist and client manuals.[55,56] No studies have been conducted exclusively targeting individuals with ADHD who are not on medication therapy.

ADHD: Brain and Executive Function Deficits

Historical Overview of the Neurologic Basis for ADHD

The neurologic basis of ADHD has evolved over the past 100 years, beginning with the definition of the disorder that focused on motor dysregulation, known as *hyperkinetic disorder of boys*. In the 1950s and 1960s, the disorder was renamed *minimal brain damage* or *minimal brain dysfunction* (MBD) and, although it was a poorly

defined term, Larry J. Seidman, Ph.D., stated that this was an important transition that placed a neurologic emphasis on the disorder. As attention and executive deficits began to be observed in the 1970s and 1980s through formal testing, the disorder became known as *attention deficit disorder* (ADD) in the Diagnostic and Statistical Manual, Third Edition (DSM-III).[57] This definition focused on the attentional networks in the brain in areas such as the PFC, parietal cortex, cingulate, callosum, thalamus, and brain stem, as well as a number of other areas.

In the last 15 to 20 years, according to Dr. Seidman, the focus has been on executive functions, which are thought to be regulated largely in the PFC, particularly in the dorsolateral PFC, as well as the cerebellum. Executive functioning is strongly linked to dopamine, a neurotransmitter implicated in several disorders, and this link identifies ADHD as a neurologic disorder. Over the past 5 years, research has shown that executive function deficits do not necessarily characterize all individuals with ADHD. Dr. Seidman stated that although executive deficits are present and have negative effects, they may vary according to ADHD severity and may indicate subtypes of certain populations with and without these deficits. It is possible that reward system deficits may signal a nonexecutive function subtype.[58]

The models of brain abnormalities of ADHD reflect changes in the constructs of understanding this neurologic disorder over the last 30 years. Dr. Seidman reported that these perspectives have evolved from a focal lesion model to models involving networks and systems of different brain regions linked together. These regions regulate attention and executive function and may include the frontal, striatal, and cerebellar areas. With neurodevelopmental disorders such as ADHD, Dr. Seidman maintained that widespread dysfunctions of these systems are more likely to occur than focal lesions, which may be typical of an adult-onset illness. Therefore, frontal system abnormalities, including areas such as the PFC and the cingulate, are thought to underlie executive function disturbances and may characterize ADHD.

Defining and Assessing Executive Functions

Dr. Seidman stated that defining executive functions has proven to be difficult; a review conducted by Sergeant et al.[59] identified at least 33 different definitions. The concept of executive function derived originally from adult patients with frontal lobe lesions who typically displayed altered affect and disturbances in impulse control, attention, planning, and goal-directed behavior. Although these characteristics are not ADHD-specific, the concept of executive function may help to categorize symptoms and treat the disorder. One method of identifying the types of executive functions is to conduct a factor analysis of a variety of tests, which suggests 4 functions: response inhibition, working memory, set shifting, and interference control.

The word *attention* is typically used to describe a cognitive function, said Dr. Seidman, whereas the DSM-IV-TR[60] definition of ADHD is based on behavior, which allows for the subtyping of patients with ADHD. The DSM-IV-TR[60] has incorporated some executive function concepts and divided ADHD into 2 subtypes: inattentive and hyperactive/impulsive. Barkley[61] proposed the hypothesis that the dorsolateral PFC may be associated with the inattentive subtype, while the ventral orbitofrontal cortex may be associated with the hyperactive/impulsive subtype. Subtypes of ADHD assessments include cognitive or behavioral measures of executive function, which partially overlap in laboratory measures but are not entirely isomorphic. For example, less than 50% of patients with ADHD have executive function deficits on neuropsychological assessments,[62–64] a finding that emphasizes the importance of accurately distinguishing between behavioral and cognitive domains on laboratory psychological measures (J. Biederman, unpublished data, 2006). As a result, individual diagnosis should not be predicted by neuropsychological assessments, but instead should be defined by the current DSM criteria. Then, patients may be subgrouped on the basis of individual functional characteristics according to attention and executive dysfunctions.

The Empirical Neurologic Basis of Executive Functions

Analyses of executive function deficits have guided observations of structural brain abnormalities in ADHD and have emphasized social dysfunction in patients with these impairments. Many regions of the brain have been hypothesized to be abnormal based on neuropsychological studies and Dr. Seidman stated that there is growing evidence that ADHD has a neurologic basis that can be measured in brain structure and function.

Dr. Seidman reported that a number of MRI studies[4–7,65] of children with ADHD have consistently found a smaller overall cortex; smaller PFC, especially the dorsolateral PFC; reductions in the corpus callosum; and alterations in the cerebellum and the basal ganglia, especially the caudate. Several of these regions—the PFC, anterior cingulate, caudate, and cerebellum—have also been shown to be functionally abnormal on the basis of positron emission tomography (PET) and fMRI measures.[10,66,67]

In a structural MRI study[68] of adults with ADHD, Dr. Seidman and colleagues demonstrated prominent differences in the overall PFC, particularly the dorsolateral PFC and anterior cingulate, with as much as a 14% reduction in volume. Further analysis of the same subjects showed decreased cortical thickness, especially in the right hemisphere of the brain.[9]

Dr. Seidman explained that boys and girls with ADHD have been found to have the same executive function impairments.[69] Studies[69] of adolescents and adults with ADHD have shown executive function impairments to be

stable, relative to those in controls at the same age. However, Dr. Seidman and colleagues[70,71] showed that executive function impairments are more severe in children with ADHD and psychiatric comorbidities, such as learning disorders, than in children with only ADHD. Further, the comorbid subgroup is at a greater risk of developing academic and social difficulties.[71]

Implications for Social-Occupational Functioning

Executive function deficits have real-world functional meanings for patients with ADHD relevant to problem-solving as well as effective living, working, and schooling in the community. For example, explained Dr. Seidman, subtypes of patients who have executive function deficits have been shown to have considerable social-occupational impairment.[63,64] In a study of largely unmedicated adults, Seidman et al.[72] found that working adults with ADHD have a lower occupational level than adults without ADHD, even when IQ levels are comparable.

Although more characteristic of children with ADHD than adults with ADHD, executive deficits may present in tests of vigilance and sustained attention, motor inhibition, perseveration, cognitive inhibition, processing speed, working memory, and organization and planning.[73–75] Dr. Seidman pointed out that inhibition measures, such as the Stroop test or the stop-signal test, in which children with ADHD perform poorly may lead to impaired learning and memory and thus, may impair IQ and academic achievement test performance.

Limitations of ADHD Studies

Dr. Seidman stated that a number of limitations exist concerning studies of executive deficits. One limitation is the lack of long-term, follow-up studies of neuropsychological functioning in patients with ADHD. Because adults are typically self-referred, another limitation is that adult samples tend to present ADHD differently than children. This difference in presentation between adult and child ADHD should be investigated. Additionally, executive functioning of adults with ADHD over the age of 40 years and patients with ADHD onset after the period defined by the DSM (onset by 7 years at present) are other areas in which further research is needed. For example, if someone has ADHD onset at age 15 years, Dr. Seidman asked, is that a true ADHD diagnosis, and to what extent are there impairments in executive function? In studies[76] of group differences of executive function, the results are modest yet consistent in reporting effect sizes in the moderate range. For example, by comparison, these effect sizes may be one half to one third the effect sizes shown in disorders like schizophrenia.[77]

Another area for future research, Dr. Seidman stated, concerns pharmacotherapy and its effect on executive function. A naturalistic study (J. Biederman, unpublished data, 2006) reported that patients with ADHD who are not treated with stimulants perform more poorly and have worse outcomes than those individuals with ADHD who do receive medication. In this study, the results suggested that stimulants had an effect on some but not all executive functions, indicating a need for further research in this area.

Conclusion

Dr. Seidman emphasized that impairments in attention and executive function are found in many disorders in psychiatry and neurology, in neurodevelopmental and acquired disorders, and in medical disorders that may involve the PFC. ADHD is understood as a neurodevelopmental disorder typically characterized by executive function deficits. However, while these deficits are common, only about 30% to 50% of patients with ADHD have these neuropsychological impairments. The literature indicates heterogeneity of executive function deficits, a finding that may lead to revisions of the executive function theory of ADHD. Other subgroups of patients with ADHD have been proposed including those with primarily reward system deficits. Dr. Seidman reiterated that executive function deficits may be related to structural brain abnormalities in the PFC and the anterior cingulate. Further, preliminary data suggest that medications may only partially ameliorate executive function deficits.

The Impact of Different Formulations of Stimulant Medications on Abuse Liability

The Effect of Stimulant Medication on Dopamine

Thomas J. Spencer, M.D., began by explaining the interaction of medications and neurotransmitters within the brain, starting with the dopamine neurotransmitter. Dopamine is synthesized from amino acids packaged in storage vesicles. When there is a signal in the presynaptic neuron, these vesicles release dopamine into the synaptic cleft, where dopamine attaches to postsynaptic receptors and causes the signal to be transmitted. Dopamine then attaches to a transporter protein, which brings it back to the presynaptic neuron, resulting in lower synaptic concentration of dopamine. The dopamine transporter controls dopamine in the striatum, a regulatory part of the brain, as well as throughout the brain including the frontal lobes.[1]

Stimulants act by blocking the transporter, therefore inhibiting the active movement of dopamine across the synapse back to the presynaptic neuron (Figure 1). As a result, there is more dopamine and dopamine lasts longer in the synapse, which Volkow et al.[78] described as the amplification of dopamine signaling and suggested that this process would enhance task-specific signaling. Dopamine decreases background neuronal firing and increases signal-to-noise in target neurons, factors that are thought to improve attention and decrease distractibility in patients with ADHD.[78]

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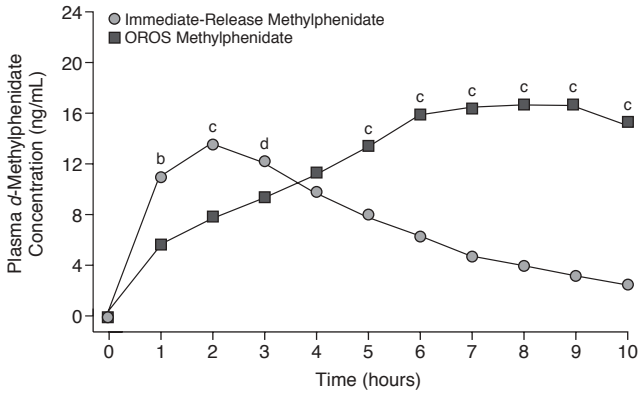
Dr. Spencer emphasized that concerns remain as to the addictive potential of stimulants in clinical practice because these medications share the same mechanism of action at the dopamine receptor as cocaine. Studies[79,80] have demonstrated similar euphoric effects of methylphenidate and cocaine when administered intravenously or by insufflation; however, when administered orally, methylphenidate does not appear to produce the reinforcing effects associated with euphoria.[81] Yet, concerns persist about the oral use of stimulant medications. In a review[82] of 60 studies, 80% indicated that methylphenidate generated subjective responses indicative of abuse potential or acted functionally similar to a reinforcing agent, e.g., dextroamphetamine or cocaine. Further, the rate of absorption may be a critical moderator in determining the abuse liability risk of oral formulations of methylphenidate.[83,84]

Figure 2. Mean Plasma *d*-Methylphenidate Concentrations in Healthy Subjects After a Single Dose of Immediate-Release or OROS Methylphenidate[a]



[a]Reprinted with permission from Spencer et al.[83]
[b]Significant difference between groups (F = 8.62, df = 1,22; p < .01).
[c]Significant difference between groups (F = 16.3–198, df = 1,20–22; p < .001).
[d]Significant difference between groups (F = 6.27, df = 1,22; p < .05).

Abuse Liability of Stimulants

A study[83] conducted by Dr. Spencer and colleagues compared immediate-release methylphenidate, which is rapidly introduced into the bloodstream and to the brain, with OROS methylphenidate, which is an osmotic system meant to produce a gradual delivery of the medication through 8 hours to provide duration of effect through 12 hours. Doses of 40 mg of immediate-release methylphenidate and 90 mg of OROS methylphenidate were chosen to match the peak of medicine or equivalent maximum concentration (C_{max}). Hourly assessments were conducted using the Drug Rating Questionnaire, a scale that has been effective in determining the abuse liability of methylphenidate,[82] to evaluate participants' subjective measure of drug effect, liking of the drug, and disliking of the drug. The study sample consisted of 12 volunteers with no history of DSM-IV diagnosed disorders, no current or past drug abuse, and no exposure to psychotropic medications or tobacco.

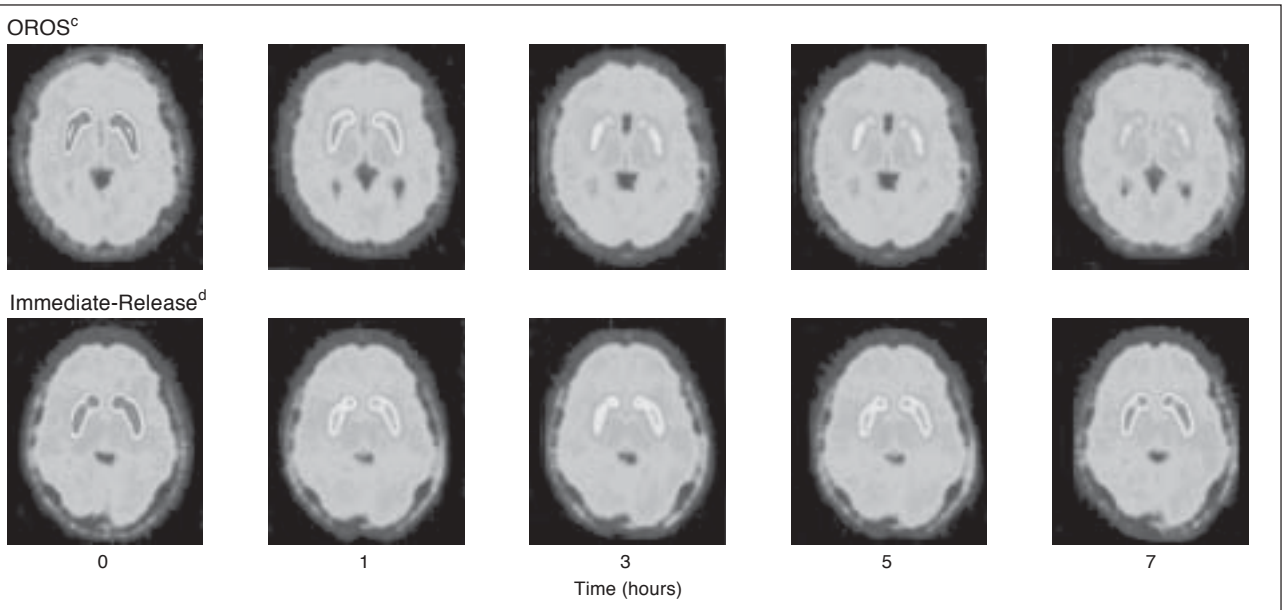
The results indicated that Dr. Spencer and colleagues were correct in their predictions of dosage; the immediate-release methylphenidate had an early peak, while OROS methylphenidate gradually increased in concentration and peaked around the 7- to 8-hour mark (Figure 2).[83] These results signify that both medications achieved the same dopamine occupancy in the brain, although at different times. A comparison of the serial PET scans of 2 healthy patients who took immediate-release methylphenidate versus OROS methylphenidate shows the level of dopamine occupancy of the medication throughout the time range (Figure 3).[83] At hours 1 to 3, the immediate-release methylphenidate dopamine transporter occupancy was 70%; however, in hours 5 to 7, occupancy dropped to 50% then to 40%. OROS methylphenidate reached 50% dopamine occupancy by hour 1 and continued to increase throughout the assessment process until hour 7 when 70% occupancy was achieved (all percents are approximate).

According to the Drug Rating Questionnaire, individuals who were administered immediate-release methylphenidate reported greater response scores on all of the 3 assessments than participants taking OROS methylphenidate: they felt more early on, liked the effects of the medication more, and reported more disliking of the medication. With OROS methylphenidate, feelings were less intense than those with immediate-release methylphenidate. The medication has a slower velocity of plasma and central nervous system uptake, which is an important factor to consider when assessing drug abuse liability. Additionally, there was essentially no liking of OROS methylphenidate at any time. When the amount of dopamine receptor occupancy is compared with the feelings of the participants, a clear relationship is displayed for the immediate-release methylphenidate, but no such association occurs with OROS methylphenidate. Although a distinct difference was found in this study, Dr. Spencer emphasized that the abuse potential for oral methylphenidate is still quite low.

Conclusion

The study[83] conducted by Dr. Spencer and colleagues found that, despite similar peaks of dopamine occupancy in the brain, a more robust abuse liability was indexed by greater detection of and likability for immediate-release methylphenidate than OROS methylphenidate at any time. In fact, little detection of or likability for OROS methylphenidate was displayed regardless of comparable peak dopamine occupancy levels. These results

Figure 3. Serial PET Brain Images Showing Striatal Dopamine Transporter Receptor Occupancy After a Single Dose of Immediate-Release or OROS Methylphenidate[a,b]



[a]Reprinted with permission from Spencer et al.[83]
[b]Dopamine transporter receptor occupancy in the striatum was assessed by measuring binding of a carbon-11-labeled imaging agent (Altropane).
[c]Plasma *d*-methylphenidate concentrations in this subject were 5.8 ng/mL at 1 hour, 9.2 ng/mL at 3 hours, 13.3 ng/mL at 5 hours, and 16.1 ng/mL at 7 hours.
[d]Plasma *d*-methylphenidate concentrations in this subject were 11.1 ng/mL at 1 hour, 12.2 ng/mL at 3 hours, 7.9 ng/mL at 5 hours, and 4.8 ng/mL at 7 hours.

support the hypothesis that the velocity of methylphenidate delivery into plasma and the central nervous system is a key factor in abuse liability when considering the use of oral stimulant formulations.

ADHD: Focus on Pharmacotherapy

Timothy E. Wilens, M.D., began his presentation by stating that childhood ADHD can persist in up to 80% of adolescents[85] and 65% of adults.[86] Because of high prevalence and persistence rates, the American Academy of Pediatrics (AAP)[85] advocated initiation of a management program in the primary care setting that acknowledges ADHD as a chronic condition.

Treatment Parameters and Components for Children With ADHD

Dr. Wilens reported that the American Academy of Child and Adolescent Psychiatry[86] has established treatment parameters recommending that attention be paid to the desired results: improved academic performance; improved familial, peer, and teacher relationships; decreased disruptive behavior; increased independence in self-care or homework; and improved self-esteem. Target outcomes should be modified to improve the identified key symptoms and specific impairments, and decisions should be guided by what is best and most realistic for the patient.

Several components underlie the integrated treatment of ADHD. One aspect for families of patients is support groups like Children and Adults With Attention-Deficit/Hyperactivity Disorder (www.chadd.org) that can be easily accessed and may provide families with useful information in helping to manage this disorder. Another factor, Dr. Wilens explained, includes educational assessments of individuals with ADHD to determine the presence of learning disabilities. When patients are treated pharmacologically or behaviorally and ADHD problems continue to persist, ADHD coaching or study-skills tutoring may be an appropriate treatment option. Other components consist of combined behavioral and pharmacotherapeutic interventions, which the AAP Guidelines[85] strongly recommend using to improve outcomes for children with ADHD.

Psychotherapy for Children With ADHD

Dr. Wilens stated that some of the components of therapy for the treatment of children with ADHD that can be considered include parent training, school interventions, and social skills training. Data on the role of behavioral and/or pharmacologic treatment in ADHD is available. The Multimodal Treatment of ADHD study[87] examined the role of behavior therapy alone; pharmacotherapy alone, which included an extremely sophisticated algorithm implementation; behavior therapy in combination with pharmacotherapy; and community assessments alone. Of 579 children, all participants improved, with those children receiving medication alone and medication plus behavior therapy having improved significantly at the 2-year

follow-up. Dr. Wilens noted that an important secondary analysis showed that those children receiving combination therapy required slightly lower doses of medication (mainly stimulant), achieved more normalization, and had more improvement in anxiety symptoms compared with those children who received medication only.

Parent training. The goal of parent training is to help parents work with each other to understand their child and to make the appropriate, consistent behavioral interventions to improve positive feedback for the child's positive behaviors while diminishing negative feedback and negative behaviors. Dr. Wilens stated that this occurs through establishing a structure in the home consistent with that of the child's school. Education around patterns of behaviors, appropriate parental interventions, and improving communication are among ingredients in parent training.

School interventions. School interventions involve a number of academic-based issues in ADHD including the remediation of learning disabilities or dysfunction, the coordination of special education for children with ADHD who may be eligible for such measures,[88] the ongoing assessment of the presence and response to treatment of ADHD, and behavioral interventions in youth with behavioral dysregulation as part of their ADHD. By setting clear and well coordinated goals between school personnel and parents, a uniform structure exists that is helpful to the child's success. This structure includes evaluating, managing, and intervening in destructive behaviors. Dr. Wilens emphasized the importance of collaboration between parents and teachers to ensure that the child turns in homework regularly, is attentive during the day, understands new assignments, and has the appropriate assignments to work on at home. Further, coordination with the school needs to include regular evaluations of the child's academic performance and achievement, overall learning ability, fund of knowledge, and peer interactions.

Social skills training. Social skills training aims to improve children's ability to communicate, to understand their own and others' feelings, to talk and play with their peers, to manage their frustration and anger, and to help them develop coping strategies during days of difficulty or poor mood.[88] While social skills training has been demonstrated to be helpful acutely, the generalization of the acute effects in the classroom and schoolyard has yet to be demonstrated.

Pharmacotherapy for Children With ADHD

In addition to behavior therapy, Dr. Wilens acknowledged that there is a growing armamentarium of medications available for treating children with ADHD. Stimulants and atomoxetine have been approved by the U.S. Food and Drug Administration (FDA) and other medications such as wakefulness agents, antidepressants, and antihypertensives have also proven to be effective, although these medications are not approved by the FDA for the treatment of ADHD.

Stimulants. Stimulants have been shown to improve the core symptoms of ADHD—inattention, impulsivity, and hyperactivity—as well as improve medication compliance, impulsive aggression, social interactions, and academic efficiency and accuracy.[88]

With regard to choosing among stimulant medications, Dr. Wilens recommended opting for the once-daily preparations that typically last from 8 to 12 hours. These extended-release formulas provide medication coverage during school as well as extracurricular activities, which may involve driving, socializing with friends, or completing homework. Additionally, problems with in-school dosing are avoided, possibly thwarting privacy and controlled substance issues. Students tend to display less academic and behavioral extremes throughout the day with extended-release medications compared with immediate-release medications and in one study,[89] extended-release was the preferred medication. Immediate-release medications can be associated with misuse, abuse, and diversion as evidenced by studies of stimulant misuse in adolescents,[90,91] young adults,[90] and college students[92]; extended-release medications may reduce this substance misuse/abuse.

According to the AAP Guidelines,[85] when initiating stimulant pharmacotherapy clinicians should begin with the appropriate starting dose and then continue to use higher doses to achieve the optimal dose with the best individualized response and least adverse side effects. Accordingly, doses should be based on an individuals' personal needs and responses to the medication. For example, one study[93] indicated that low doses of methylphenidate produced improvements in neuropsychiatric testing, rating scales of ADHD, behavior efficiency, and percentage of time on a task. However, higher doses related to even more drastic improvements in these assessments, signifying the importance to accurately dose medications. Similarly, a study[94] of OROS methylphenidate showed that 37% of the adolescent subjects required the maximum dosage (72 mg) in order to achieve a 30% reduction in ADHD symptoms.

No parameters can predict optimal dosage or timing, including weight, age, gender, or severity of illness. Dr. Wilens stressed that if one stimulant does not induce patient response, a different stimulant should be considered unless a nonstimulant medication, such as atomoxetine, is the best alternative. Regular monitoring of patients during this time is necessary to ensure the effective management of ADHD symptomatology. Further, patients should also be monitored during long-term usage of stimulants to assess any adverse effects on weight and height, proper adherence and use, and effects on the cardiovascular system that can be screened using the American Heart Association Guidelines.[95]

Atomoxetine. Dr. Wilens stated that this FDA-approved medication can initially be used as monotherapy[96,97] and

may be an effective treatment for nonresponders to stimulants[98] or for partial responders that require adjunctive medications to control ADHD symptoms.[99] Additionally, atomoxetine can be used to treat individuals who experience adverse effects,[100] such as tics or weight issues, from stimulants, as well as individuals who have active comorbid substance use and who therefore may misuse or abuse stimulant medications.[101] Atomoxetine is also a good choice and has been shown to be efficacious in the treatment of ADHD with comorbid disorders, such as anxiety,[102] tics,[103] mood,[102] and substance use.[101]

Other medications. Dr. Wilens maintained that other alternative medications not approved by the FDA for the treatment of ADHD can be effective pharmacotherapy for this population. Modafinil has been shown to improve ADHD symptomatology, including attention, hyperactivity/impulsivity, and oppositional behavior, as compared with placebo.[104] Additionally, modafinil was well-tolerated with all adverse events reported being mild to moderate in severity, and no clinically significant cardiovascular risks were associated with this medication.[104]

Of the antidepressants, bupropion is helpful in treating individuals with ADHD alone[105,106] and ADHD with comorbid mood disorders, cigarette smoking, or active substance use disorders.[107] Also, tricyclic antidepressants such as desipramine or nortriptyline may be successful in treating ADHD alone or with comorbid anxiety and/or tic disorders.[106]

Antihypertensive agents, or α-adrenergic agonists, such as clonidine and guanfacine, appear to be efficacious in children and adolescents with ADHD, particularly those who have prominent impulsivity, aggression, or hyperactivity, as well as individuals who have comorbid tic disorders.[108–110] Hazell and Stuart[108] compared psychostimulant medication plus clonidine versus placebo in children and adolescents. Individuals on the combination treatment regimen showed improvements on the Conners Behavior Checklist with good tolerability. Dr. Wilens stated that methylphenidate with adjunctive α-agonists may also be effective in treating patients with ADHD and sleep disorders.

Conclusion

ADHD is a chronic but treatable disorder using ongoing multimodal approaches including behavioral treatments and pharmacotherapy. Dr. Wilens emphasized that assessments of the condition, as well as evaluations of the long-term adverse events of medications, be thoroughly examined during ongoing treatment. When treating patients with pharmacotherapy, proper titration methods and dosing should be tailored to the individual patient, taking into account the development of side effects and comorbid illnesses and disorders. In addressing comorbid conditions, Dr. Wilens remarked that, in general, the accepted practice is to treat the most severe condition first. For example, if a patient presents with ADHD and severe major depressive disorder, the depression would be considered primary and the ADHD secondary. Physicians should consider the use of dual-action agents, such as atomoxetine for ADHD and anxiety or clonidine for ADHD and tic disorders. In subjects who have ADHD and comorbid substance use disorder, Dr. Wilens recommended that the treatment of ADHD promptly follow the stabilization of the substance of use.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin and others), clonidine (Catapres and others), desipramine (Norpramin and others), dextroamphetamine (Dexadrine, Dextrostat, and others), guanfacine (Tenex and others), methylphenidate (Focalin, Concerta, and others), modafinil (Provigil), nortriptyline (Pamelor and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, atomoxetine, dextroamphetamine, and methylphenidate are not approved by the U.S. Food and Drug Administration for the treatment of depression; and bupropion, clonidine, desipramine, guanfacine, modafinil, and nortriptyline are not approved for the treatment of attention-deficit/hyperactivity disorder.

Faculty disclosure: In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity 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 grant/research support from Abbott, Bristol-Myers Squibb, Cephalon, Eli Lilly, Janssen, Lilly Foundation, McNeil, National Institute of Child Health and Human Development, National Institute of Mental Health (NIMH), National Institutes on Drug Abuse, Neurosearch, New River, Novartis, Pfizer, Prechter Foundation, Shire, and Stanley Medical Institute; is on the speakers bureaus for Cephalon, Eli Lilly, McNeil, Novartis, Shire, and UCB Pharma; and is on the advisory boards for Cephalon, Eli Lilly, Janssen, McNeil, Novartis, and Shire. **Dr. Seidman** has received grant/research support from NIMH, Mental Illness Neuroscience Discovery Institute, National Association for Research in Schizophrenia and Affective Disorders, and Janssen and has received honoraria from Shire. **Dr. Spencer** has received grant/research support from Eli Lilly, GlaxoSmithKline, McNeil, NIMH, Novartis, Pfizer, and Shire; is on the speakers bureaus for Eli Lilly, GlaxoSmithKline, McNeil, Novartis, Shire, and Wyeth; and is on the advisory boards for Eli Lilly, GlaxoSmithKline, McNeil, Novartis, Pfizer, and Shire. **Dr. Wilens** has received grants from, is a member of the speakers bureaus for, and is a consultant for Abbott, Alza/Ortho-McNeil, Cephalon, GlaxoSmithKline, Janssen, Eli Lilly, National Institutes on Drug Abuse, NIMH, Neurosearch, NICMH, Novartis, Pfizer, Saegis, and Shire. **Dr. Safren** has no personal affiliations or financial relationships with any proprietary entity producing health care goods or services consumed by, or used on, patients to disclose relative to the presentation.

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