Introduction

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

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Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood, with an estimated prevalence of 5% among school-aged children.[1] ADHD often persists into adolescence and adulthood; however, prevalence data in these populations are limited. ADHD is characterized by inattention, hyperactivity, and impulsivity, all of which can lead to problems at home and at school.

Although U.S. Food and Drug Administration (FDA)–approved stimulants methylphenidate and amphetamine have been proven safe and effective for the treatment of ADHD, an estimated 30% to 50% of all children and adults with ADHD either do not respond to or do not tolerate treatment with stimulants.[2] Concern about the abuse potential of stimulants may also limit their use. For these reasons, there is considerable interest in developing effective, nonstimulant options for treating ADHD.

The selective norepinephrine reuptake inhibitor atomoxetine is the first nonstimulant medication to receive FDA approval for use in both children and adults for the treatment of ADHD. Other pharmacologic options include the stimulant pemoline, the antidepressants bupropion and desipramine, and the antihypertensives clonidine and guanfacine.[3] Selecting the appropriate pharmacologic regimen can be difficult, and lack of response or the appearance of adverse events may limit their use. Consideration should be given to the patient's daytime and evening schedule.

NEW DEVELOPMENTS IN TREATMENT OPTIONS

Ongoing development of new ADHD treatment options emphasizes alternative and extended-release delivery systems and nonstimulant compounds. Three novel treatments that are of particular interest and showing promise for the treatment of ADHD at the present time are guanfacine, a methylphenidate transdermal patch, and modafinil film-coated tablets.

Guanfacine

Guanfacine, an α_2-adrenergic receptor agonist, has had mixed results in the treatment of ADHD. Although guanfacine has been shown to have cognitive-enhancing properties,[4,5] in a recent study[6] of its effect on executive function and memory, 60 healthy males were randomly assigned guanfacine in double-blind fashion at a single dose of 1 mg, 2 mg, or placebo. No statistically significant effects on any cognitive measures were observed, but negative effects on blood pressure and a mild sedative effect were reported, possibly owing to mechanisms of autoreceptor down-regulation.

On the other hand, guanfacine has been shown to be effective at treating the classic symptoms of ADHD, i.e., inattention, hyperactivity, and impulsivity. A retrospective chart review[7] of 80 children and adolescents with pervasive developmental disorders (hyperactive and inattentive types) who had received guanfacine (mean ± SD daily dose = 2.6 ± 1.7 mg [range, 0.25–9.00 mg]) for an average of 334 days (range, 7–1776) revealed symptom improvement in all 3 ADHD symptoms. Guanfacine was well tolerated and did not lead to significant changes in blood pressure or heart rate. Earlier trials of guanfacine in children with ADHD and tic disorders[8,9] and adults with ADHD[5] have also reported guanfacine to be safe and well tolerated.

Guanfacine is of particular interest for its use in patients with ADHD who are vulnerable to the abuse liability of stimulants. At the same time, increasing interest in combining nonstimulants with stimulants to enhance treatment effects may lead to more controlled trials on the safety and efficacy of both guanfacine and its use in combination with stimulants.[3,10]

Methylphenidate Transdermal System

Oral methylphenidate has long been a first-line treatment for symptoms of ADHD, but for some, especially children, the delivery of an oral medication during school

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or extracurricular activities often presents a challenge. Transdermal technology could ease this problem. Phase 2 and 3 clinical trials of a methylphenidate patch that delivers continuous medication release throughout the day have shown the methylphenidate transdermal system (MTS) to be generally well tolerated. Adverse events in these trials were consistent with known effects of methylphenidate and were typically mild to moderate.

A recent study[11] of transdermal methylphenidate in children has shown that use at low doses (12.5 cm^2, 25.0 cm^2, and 37.5 cm^2) and in combination with behavior modification yielded better results than either treatment alone. Another dosing study in children[12] was designed to measure efficacy and the influence of exposure time on morning effects. Methylphenidate transdermal system (0.45 mg/h, 0.9 mg/h, or 1.8 mg/h) or placebo was randomly assigned to 36 children with ADHD (age range, 7–12 years) in a multicenter, double-blind design. Several findings were reported: the time of application did not significantly affect daily behavior, the highest dose produced limited incremental benefit compared with the midrange dose, and the formulation was well tolerated. Methylphenidate transdermal system is a treatment option on the horizon that may affect future delivery mechanisms for other medications as well. Methylphenidate transdermal system is currently under review by the FDA.

Modafinil Film-Coated Tablets

Another ADHD treatment under investigation is a new formulation of modafinil. Modafinil has been approved by the FDA to improve wakefulness in patients with excessive sleepiness associated with narcolepsy and for treating shift work sleep disorder and obstructive sleep apnea. Since the core symptoms of ADHD may be related to deficits of attention, the alerting effects of modafinil make it a candidate for further research in ADHD.

The pharmacologic profile and structure of modafinil are notably different from those of stimulants and other agents used to treat ADHD, and modafinil may reduce the core symptoms of ADHD via the same mechanism by which it improves wakefulness—selective activation of the cortex without generalized effects on the central nervous system. This mechanism results in reduced abuse potential and less likelihood of jitteriness, anxiety, or excess locomotor activity than traditional stimulants.

Recent placebo-controlled studies[13,14] of modafinil film-coated tablets in children and adolescents (age range, 6–17 years) provide evidence that this formulation, administered once daily, may improve the full spectrum of symptoms of ADHD. Both studies were multicenter, double-blind, and placebo-controlled. The first was a 7-week study[13] of modafinil film-coated tablets administered at fixed doses once daily. In this study, 190 patients with ADHD were randomly assigned to modafinil (340 mg/day in patients weighing < 30 kg [N = 44]; 425 mg/day for patients weighing ≥ 30 kg [N = 82]) or placebo (N = 64). The second was a 9-week study[14] of modafinil film-coated tablets administered as flexible doses (range, 170–425 mg/day) administered once daily in the morning. The dose was individually titrated to an optimal dose based on efficacy and tolerability. The mean stable daily dose was 368.5 mg/day, and the median was 425 mg/day. Outcomes of both studies were similar. Modafinil significantly improved symptoms of ADHD compared with placebo as measured by reduced scores on the ADHD Rating Scale IV (School and Home Versions) and ratings of "much improved" or "very much improved" on the Clinical Global Impressions-Improvement scale of overall clinical condition. In addition, the fixed-dose study[13] included a 2-week, double-blind observation period after abrupt discontinuation of modafinil. No symptoms of withdrawal or rebound of ADHD symptoms were observed. Both studies showed that modafinil film-coated tablets were well tolerated, with the most common adverse events being insomnia, headache, and decreased appetite, all of which wane over time. Neither study showed any statistically significant or clinically meaningful effects for the majority of patients on measures of cardiovascular function, including heart rate and blood pressure. These findings suggest that modafinil may provide a novel therapeutic option for the management of ADHD in pediatric and adolescent patients.

NEW DEVELOPMENTS IN THE PATHOPHYSIOLOGY OF ADHD

In an effort to better understand the pathophysiology of ADHD, recent research has focused on identifying the etiology of ADHD. These studies have revealed that ADHD is highly heritable and may be associated with neurobiological deficits in the prefrontal cortex and related subcortical systems. As the causes and course of ADHD are better understood, newer and more selective medications are being developed for ADHD.

A review of new developments in the treatment of ADHD means discussing not only medications that have been found useful but also recent research findings about the neurobiology of the disorder, the presentation and impact of the disorder and comorbid diagnoses, the mechanisms of action of medications that can be used to treat the disorder, and outcomes of nonpharmacologic strategies. In addition, understanding the role that primary care physicians play in treatment of the disorder allows comprehensive, multimodal management to be provided to patients and their families for the best possible outcome.

First, Amy F. T. Arnsten, Ph.D., provides a biological background for the discussion of the disorder. According to neuropsychological and imaging study findings, ADHD is associated with alterations in the prefrontal cortex (PFC) and its connections to the striatum and cerebellum. Both animal research and human observation have shown that

the PFC is critical for the regulation of behavior, attention, and affect and is important for sustaining attention over a delay, inhibiting distraction, and dividing attention. More posterior cortical areas are essential for perception and the allocation of attentional resources, and the PFC in the right hemisphere is especially important for behavioral inhibition. Lesions to the PFC produce distractibility, forgetfulness, impulsivity, poor planning, and locomotor hyperactivity. The PFC is very sensitive to its neurochemical environment, and optimal levels of norepinephrine and dopamine are needed for proper PFC control of behavior and attention. Thus, some therapeutic effects of stimulant medications may occur through increasing endogenous stimulation of α_{2A}-adrenoceptors and dopamine D_1 receptors in the PFC.

Stephen V. Faraone, Ph.D., and Sajjad A. Khan, Ph.D., continue the discussion of the neuropathology of ADHD. The molecular genetics and behavioral literature indicates that both genetic and environmental factors may contribute to the development of ADHD. Family, twin, and adoption studies provide compelling evidence that genes play a strong role in mediating susceptibility to ADHD. Molecular genetics studies suggest that the genetic architecture of ADHD is complex, while the few genome-wide scans conducted thus far are not conclusive. However, the many candidate gene studies have produced substantial evidence implicating several genes in the etiology of ADHD: the dopamine D_4 receptor gene (*DRD4*), the dopamine D_5 receptor gene (*DRD5*), the dopamine transporter gene (*DAT*), the dopamine β-hydroxylase gene (*DBH*), the serotonin transporter gene (*5-HTT*), the serotonin receptor 1B gene (*HTR1B*), and the *SNAP25* gene. Recent pharmacogenetic studies have correlated treatment nonresponse with particular gene markers, while preclinical studies have increased our understanding of gene expression paradigms and potential analogs for human trials.

Next, Alysa E. Doyle, Ph.D., reviews empirical studies examining executive functions in ADHD populations. Dr. Doyle notes that although ADHD is associated with impaired performance on measures of response inhibition, working memory, and other aspects of executive functions, data also suggest substantial neuropsychological variability within and across ADHD samples. Executive function deficits are etiologically linked to ADHD but are not the single underlying deficit in the disorder. She concludes that ADHD may be best conceptualized as a neuropsychologically heterogeneous condition.

Shifting from neurobiology and theoretical models to presentation and impact of the disorder, Thomas J. Spencer, M.D., describes the negative impact of ADHD on children and highlights the frequency of comorbid mood, anxiety, oppositional defiant, and conduct disorders, which are highly related to poorer illness course and outcome. Dr. Spencer also points out that research has shown that, compared with controls, children with ADHD perform more poorly in school, have increased prevalence of developmental disorders, and have an increased risk of cigarette smoking and substance abuse during adolescence.

Because of potential outcomes such as those described by Dr. Spencer, appropriate treatment is important for patients with ADHD. Timothy E. Wilens, M.D., addresses the mechanisms of action of medications that have been demonstrated to be effective treatments for ADHD. Both the stimulant and nonstimulant medications that are efficacious in ADHD appear to either directly or indirectly attenuate dopamine and norepinephrine neurotransmission, although differences exist both between and within the specific classes of agents. Dr. Wilens predicts that understanding the various mechanisms of action of ADHD medications may help practitioners select agents on the basis of patient characteristics (e.g., genotype).

Margaret D. Weiss, M.D., Ph.D., Kenneth Gadow, Ph.D., and Michael B. Wasdell, M.A., address the differences between patients in drug efficacy trials and those seen in the clinic. Effectiveness studies, such as practical clinical trials and naturalistic follow-up studies, are needed to truly examine drug impact in the real world.

Although ADHD is primarily treated with medications, Steven A. Safren, Ph.D., notes that residual symptoms may be amenable to a structured, cognitive-behavioral treatment approach. Dr. Safren reviews the extant research on outcome studies of psychosocial interventions for adults with ADHD and presents a model for the treatment of residual ADHD in adults and, potentially, adolescents.

Finally, Larry Culpepper, M.D., M.P.H., shares insight about the role played by primary care physicians in the management of ADHD. When first encountering a new patient with ADHD, primary care physicians should confirm the diagnosis, identify comorbidities and other primary disorders, and comprehensively assess the patient, which includes consideration of family-related influences. Because the long-term management of multiple medical, mental health, and psychosocial problems is often ineffective if ADHD is inadequately treated, multimodal management is needed.

The expert faculty assembled in this supplement offer insights to improve clinical practice and to stimulate future research in ADHD. The new developments described herein should help clinicians and investigators optimize outcomes for patients with ADHD.

Drug names: amphetamine (Adderall and others), atomoxetine (Strattera), bupropion (Wellbutrin), clonidine (Catapres), desipramine (Norpramin), guanfacine (Tenex), methylphenidate (Ritalin, Metadate, and others), modafinil (Provigil).

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

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