Adult Attention Deficit Disorder
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PHYSICIAN'S REFERENCE: TREATMENT & MEDICATIONS RESEARCH: CURRENT CONCEPTS & FUTURE DEVELOMENTS

By David W. Goodman, MD

PHARMACOTHERAPY OF ADULT ATTENTION DEFICIT / HYPERACTIVITY DISORDER

Program Overview

Attention Deficit/Hyperactivity Disorder (ADHD) is a commonly diagnosed psychiatric disorder that leads to significant impairment across the lifespan. Although historically defined as a childhood disorder, the adult manifestation has more recently been identified; yet, many adults with this disorder remain unidentified and untreated. This series of 15 short articles provide brief overviews of important topics on the diagnosis, management, and treatment of patients with ADHD. These articles will provide the practicing clinician current information relevant to the treatment of their patients with ADHD.

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Director, Adult Attention Deficit Disorder Center of Maryland; Assistant Professor, Johns Hopkins School of Medicine, Department of Psychiatry and Behavioral Sciences, Johns Hopkins at Green Spring Station.
Disclosures: David W. Goodman, MD, has disclosed that he has received research grants from Forest Laboratories, Shire Pharmaceuticals, Ortho-McNeil Pharmaceutical, Cephalon Inc., New River Pharmaceuticals, and Eli Lilly and Company. He has also disclosed that he has received honoraria from Forest Laboratories, Eli Lilly and Company, Shire Pharmaceuticals, Ortho-McNeil Pharmaceutical, and Wyeth Pharmaceuticals and is a member of Speakers Bureaus sponsored by Forest Laboratories, Shire Pharmaceuticals, Ortho-McNeil Pharmaceutical, and Wyeth Pharmaceuticals. He receives royalties from MBL Communications.

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Intended Audience
This activity has been developed for psychiatrists and other mental health professionals involved in the care of adult patients with attention-deficit/hyperactivity disorder.

Goal
The purpose of this CME activity is to provide information and recommendations about incidence as well as identification and management of adults and children with attention-deficit/hyperactivity disorder with or without comorbid psychiatric conditions.

Educational Objectives
After completing this activity, participants should be better able to:
Identify the drugs that are approved for the treatment of ADHD in adults, as well as unapproved but commonly used drugs, and describe the evidence for their efficacy and safety.

Choose appropriate medications for their adult patients with ADHD.
Release Date of Activity: June 15, 2009
Expiration Date of Activity for AMA PRA Credit : June 15, 2010
Estimated Time to Complete This Activity: 0.5 hour

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Outcomes Participation

To better define and meet the CME needs of health care professionals and enhance future CME activities, EOCME will conduct an outcomes-measurement survey following the conclusion of the program. This follow-up survey is designed to measure changes to attendees' practice behaviors that are a result of their participation in this CME activity. You will be contacted by email 30 days following the conclusion of this activity with an outcomes-measurement survey. We would greatly appreciate your participation.

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INTRODUCTION

The safety and efficacy of established therapies for the treatment of attention deficit/hyperactivity disorder (ADHD) in children and adolescents have been documented for nearly 70 years.1 Since Bradley's seminal report of the benefit of Benzedrine in disruptive children in 1937, more than 200 controlled trials have demonstrated the efficacy of methylphenidate and amphetamine in children and adolescents. However, most of the clinical investigation of ADHD treatments in adults has occurred only in the past 10 to 15 years. It has been estimated that approximately 50% of children diagnosed with ADHD will continue to have symptoms into adulthood and may need medication as adults.2

The current FDA-approved medications for adult ADHD are long-acting stimulants and atomoxetine. For adults, amphetamine stimulants are prescribed most frequently, in part because mixed amphetamine salts was the first stimulant to receive FDA approval (in 2004) for adult ADHD. The first methylphenidate preparation approved for adult ADHD was dexmethylphenidate, in May 2005. Among the available ADHD medications, only long-acting agents are approved; these are (in order of approval) atomoxetine (Strattera), extended-release mixed amphetamine salts (MAS XR [Adderall XR]), extended-release dexmethylphenidate (d-MPH XR [Focalin XR]), lisdexamfetamine (LDX [Vyvanse]), and OROS methylphenidate (OROS-MPH [Concerta]). Although they are used frequently in adults, no short-acting stimulant has been approved by the FDA for adult ADHD. Double-blind studies in which adults with ADHD were treated with bupropion, desipramine, or guanfacine have produced favorable results, but their use remains "off label." The medications discussed herein have been approved by the FDA for the treatment of ADHD in adults. (They appear in chronological order of FDA approval.)

ATOMOXETINE

In November 2002, the FDA made atomoxetine the first drug approved for the treatment of ADHD, thereby legitimizing the treatment of this age population. Atomoxetine is a selective norepinephrine reuptake transporter inhibitor, primarily metabolized by the 2D6 isoenzyme in the liver.3 Although the mean half-life of atomoxetine in most person is 3.6 hours, 5-10% of Caucasians are slow metabolizers of the drug, leading to a mean half-life of 21 hours.4 Downward dose adjustments may be necessary for slow

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metabolizers or patients on concomitant 2D6 inhibitors (ie, fluoxetine, paroxetine, or bupropion).

An initial pilot trial with a controlled crossover design was conducted by Spencer and colleagues to evaluate atomoxetine in adult ADHD.5 Dosing of atomoxetine up to 80 mg daily produced significant improvements in both ADHD symptoms and executive functioning.5 Two subsequent adult trials included a total of 536 subjects in identical, randomized, double-blind, placebo-controlled, 10-week designs.6 In these two large-scale trials, atomoxetine was found significantly superior to placebo in improving ADHD.6 The effect size was 0.35 and 0.40 for these studies, based on the primary outcome measure of investigator-rated Conners' Adult ADHD Scale. The greater effect size of 0.71 in the child studies was in contrast to the adult effect size, which was due to the larger placebo response in the adult studies.3

At the end of the two adult acute trials, 384 subjects enrolled in an open-label, long-term extension study to evaluate the ongoing efficacy and safety of atomoxetine.7 Safety was assessed by adverse events (AEs), electrocardiogram results, and laboratory testing. Doses of atomoxetine ranged from 60 to 120 mg daily, with a mean daily dose of 98.6 mg. Results at 97 weeks demonstrated that symptom improvement was maintained.
In the adult acute trials, atomoxetine was dosed twice daily and generally was well tolerated. AEs reported more frequently in the drug-treatment group than in the placebo group were dry mouth, insomnia, nausea, constipation, decreased appetite, dizziness, sexual difficulties, and urinary retention. Clinical experience suggests that urinary hesitancy in males with prostate enlargement may be a limiting side effect. Although no evidence of liver injury was detected in clinical trials, there have been two post-marketing cases of severe liver injury in patients who received atomoxetine. Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury.3

In 2005, reports of suicidal ideation in children and adolescents treated with atomoxetine led to an FDA-boxed warning similar to that for antidepressant medications, but based on the analysis of the adult studies no such warning was required for adults. Nonetheless, regardless of the choice of treatment it is prudent to be alert for suicidality in all patients with ADHD and particularly those with comorbid mood, anxiety, and substance use disorders. Non-stimulants are used as second-line treatment of ADHD when the patient

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does not respond to first-line stimulant therapy, does not tolerate stimulants, or has an active substance use disorder.8,9

ADDERALL XR

In August 2004, the extended-release mixed amphetamine salts formulation, Adderall XR, received FDA approval for the treatment of adults with ADHD, becoming the first stimulant medication with this indication. Two clinical trials were conducted to prove the safety and efficacy of Adderall XR in adults. A double-blind, placebo-controlled, forced-titration, 4-week trial of Adderall XR for the treatment of adult ADHD involved 255 subjects. In this multicenter study, subjects were randomized to receive placebo or Adderall XR 20 mg/d, 40 mg/d, or 60 mg/d.10 The primary outcome measure was the ADHD Rating Scale as rated by the investigator. The authors reported statistically significant improvement in ADHD rating scores in all Adderall XR treatment groups compared with placebo ($p<.001$). The mean total reduction in ADHD Rating Scale scores, which reflected significant decreases in both inattention and hyperactivity/impulsivity symptoms, were: placebo, 6.6 points; MAS XR 20 mg/d, 12.6 points; MAS XR 40 mg, 12.9 points; and MAS XR 60 mg, 14.4 points. Among the subjects rated as "very much improved" and "much improved" on the Conners' Global Impressions of Improvement, there was a significant dose response for efficacy. For the subjects with severe ADHD (defined by an ADHD Rating Scale score of ≥32), Adderall XR 60 mg/d significantly reduced the rating score compared with placebo and Adderall XR 20 mg/d. There was no dose relationship for any AE except dizziness. The most common treatment-related AEs experienced by adults were dry mouth, anorexia/decreased appetite, insomnia, headache, nervousness, weight loss, nausea, agitation, and anxiety.

Following the 4-week acute trial, 223 subjects enrolled in a long-term, open-label, flexible-dose trial, starting on Adderall XR 20 mg/d. During the first 2 months, dosing was optimized. The 24-month interim analysis showed a sustained reduction of ADHD symptoms.11 Dose adjustments generally occurred in the first 3 months, with few dose changes thereafter. Sustained improvement over 24 months, with few dose adjustments, supports the impression that tolerance to Adderall XR did not develop.

DEXMETHYLPHENIDATE

Dexmethylphenidate was approved for child, adolescent, and adult ADHD in May 2005. Spencer and colleagues conducted a double-blind, placebo-controlled, 5-week trial with extended-release dexmethylphenidate in 221 adults with ADHD.12 Subjects were randomized to receive daily doses of 20,

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30, or 40 mg. Using the ADHD-RS IV as the primary measure, doses of 20, 30, and 40 mg significantly reduced the subjects' scores, by 13.7, 13.4, and 16.9, respectively. Responses rates, defined as a reduction of more than 30% in the ADHD-RS IV, were 34% for placebo, 57.9% for 20 mg/d (p=.006), 53.7% for 30 mg/d (p=.012), and 61% for 40 mg/d (p<.001). The most commonly reported AEs related to drug treatment were headache, decreased appetite, dry mouth, and insomnia.12 (A single dose of dexmethylphenidate XR mimics the pharmacokinetic profile of two doses of dexmethylphenidate immediate-release formulation administered 4 hours apart, with less fluctuation in plasma concentration.13)

LISDEXAMFETAMINE

In April 2008, the FDA approved the use of a new once-daily stimulant, lisdexamfetamine dimesylate (LDX), in adults. The first long-acting prodrug indicated for the treatment of ADHD in children and adults, LDX is a therapeutically inactive molecule that after oral ingestion is converted by enzyme(s) from the red blood cell to l-lysine, a naturally occurring essential amino acid, and active dextroamphetamine (d-amphetamine), which is responsible for the drug's therapeutic activity. In a 4-week, double-blind, placebo-controlled, parallel-group study in 420 adults (aged 18-55 years) with a primary diagnosis of ADHD, reductions from baseline in ADHD Rating Scale among LDX-treated subjects were 16.2 (30 mg), 17.4 (50 mg), and 18.6 (70 mg), all of which were significantly better than placebo (p<.0001).14 The respective effects sizes were 0.73, 0.89, and 0.99. Clinical Global Impressions scores also were significantly greater with three doses of LDX than with placebo (p<.01). The most common AEs were decreased appetite, dry mouth, insomnia, nausea, diarrhea, feeling jittery, and anxiety. The prodrug formulation was developed to offer reduced potential for abuse-related liking effects. In a double-blind crossover study of substance-abusing adults (n=36), the increase in the "liking score" on the Drug Rating Questionnaire-Subject after 100 mg of oral LDX did not differ significantly from that after placebo, and was significantly lower than that after an equivalent dose of immediate-release d-amphetamine (p<.04).15 However, at 40 mg of d-amphetamine and 150 mg of LDX, the between-group differences in liking-score changes were not significant. A second study investigated the likeability of intravenous lisdexamfetamine compared with dose-equivalent intravenous d-amphetamine in adult stimulant abusers.16 Nine subjects received a single intravenous dose of LDX (25 or 50 mg), immediate-release d-amphetamine (10 or 20 mg), or placebo in a three-way crossover design. Although 20 mg of d-amphetamine showed significantly increased abuse-related liking scores

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compared with placebo (p<.05), the liking effects of 50 mg LDX did not differ significantly from those of placebo.

OROS METHYLPHENIDATE

In June 2008, the FDA approved for use in adults a formulation of methylphenidate (MPH) in which the drug is released via an osmotic-release oral system (OROS) for up to 9 hours. The OROS-MPH formulation, designed to deliver MPH in a controlled manner with once-daily administration, has been proven efficacious and well tolerated in children and in several recent studies of adults with ADHD.17,18 In a European randomized, double-blind, placebo controlled, forced-titration study by Medori and colleagues, 401 adults (aged 18-63 years) with ADHD received placebo or 18, 36, or 72 mg/d of OROS-MPH for 5 weeks, followed by 2 weeks at the maintenance dose.19 The primary measure of treatment response was the Conners' Adult ADHD Rating Scale. At treatment endpoint, significantly greater improvements in rating scale scores were noted for patients who received any dose of OROS-MPH relative to placebo recipients (effect sizes of .38, .43, and .62, respectively). Most AEs were mild or moderate in each treatment group, and few patients discontinued treatment because of an AE. The second study,20 conducted in the United States, was a randomized, placebo-controlled, flexible-dose study that enrolled 226 adults. Subjects assigned to the OROS-MPH arm were started on 36 mg once daily in the morning, then titrated upward by weekly 18-mg increments. Once the subject achieved a reduction of 30% or more on the investigator-rated ADHD scale and was rated "much" or "very much" improved on the Clinical Global Impression scale, that dose was maintained through the end of the trial. OROS-MPH significantly reduced ADHD symptoms on the AISRS (10.6 vs 6.8 for placebo; p<.012).20 The most common adverse reactions (>10%) reported in the pooled data of both trials were dry mouth, nausea, decreased appetite, headache, and insomnia.

ISSUES IN THE TREATMENT OF ADULT PATIENTS WITH ADHD

The concern for cardiovascular risks with ADHD medication is addressed in the package insert of each medication approved for adult ADHD. In clinical trials of all adult ADHD–approved medication, systolic blood pressure was increased by up to 5 mm Hg, diastolic pressure by up to 4 mg Hg, and pulse by up to 5 bpm.6,10,12,14,20 Although as group data this may be reassuring, outliers necessitate that vital signs be checked prior to initiating ADHD medications and regularly thereafter to ensure that no clinically relevant changes have occurred.

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Current FDA-approved medications for the treatment of ADHD in adults are listed in Table 1, along with their generic and trade names and adult dosing information.21-24 A recent study examined the total number of retail prescriptions for long- and short-acting ADHD medications generated by primary care physicians, pediatricians, and psychiatrists.25 Approximately 7 million patients in the United States filled ≥1 prescription for their ADHD in 2007. Long-acting agents accounted for 78% of ADHD prescriptions in pediatric patients (0-17 years of age) but only 49% of adult ADHD prescriptions. Despite recommendations for long-acting stimulant medication as first-line treatment for adult ADHD, 48% of the adult ADHD prescriptions are for short-acting agents. This trend will need to be addressed as more adults with ADHD are diagnosed and treated.

NON-APPROVED MEDICATIONS FOR ADULT ADHD

Randomized placebo-controlled trials in adults with ADHD have shown favorable results for bupropion, desipramine, and guanfacine, but their use remains "off label." No studies have been published on the use of clonidine in adult ADHD.

Bupropion

A blocker of dopamine and norepinephrine reuptake transporters and metabolized by 2D6 hepatic isoenzyme, bupropion has demonstrated efficacy in reducing ADHD symptoms in adults in two randomized, controlled trials. Although bupropion's treatment of adult ADHD was first published in 1990,27 it wasn't until 2001 that Wilens and colleagues reported the first double-blind, placebo-controlled, randomized, 6-week study to evaluate the efficacy of sustained-release bupropion in adults with ADHD.28 The 40 subjects enrolled had no specific mood or anxiety disorder symptoms at time of enrollment. A significant reduction in ADHD symptoms occurred in the bupropion group at week 6 (42% vs 24% for placebo). With response defined as "30% reduction in ADHD symptoms," the bupropion response rate was 76% versus 37% for placebo.

Wilens and colleagues conducted a second randomized, double-blind, placebo-controlled, flexible-dose, 8-week trial of extended-release (XL) bupropion to evaluate its efficacy in adult ADHD.29 As in the previous trial, subjects were assessed for ADHD symptoms and excluded if they had concurrent major depression, anxiety disorder, and seizure disorders. Mean daily dosing was 393 mg, with the distribution being 150 mg (1.2%), 300 mg (35.8%), and 450 mg (63%). Bupropion XL was associated with a significant reduction in ADHD symptoms at 2 weeks, which continued through the end of the trial, as

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measured by the ADHD Rating Scale. Bupropion XL appeared to be well tolerated. The rate of discontinuation due to AEs was 5% for the bupropion group (0% in the placebo group). AEs included hives and/or rash (n=2), nausea and somnolence (n=1), and irritability (n=1). There were no significant differences in AE reporting between the bupropion XL and placebo groups. No seizures occurred. With regard to seizure risk, sustained-release bupropion was evaluated in a prospective, 105-site, 1-year study, including 3100 patients with a DSM-III-R diagnosis of depression without a history of eating or seizure disorders.30 With a dosing range of 50 to 150 mg bid, only three seizures occurred among 3094 patients (0.10%).

Desipramine

The only randomized, double-blind, placebo-controlled study of a tricyclic antidepressant (desipramine) in adult ADHD demonstrated significant improvement in symptoms (68%) using a pre-established definition of improvement: CGI score of 1 (very much improved) or 2 (much improved) plus a reduction in ADHD rating scale of 30% or better ($p<.0001$).31 The mean dose was 171.1 mg/d for week 2, 161.1 mg/d for week 4, and 147.4 mg/d for week 6. There was no relationship between response and the dose of desipramine. The most common AEs were dry mouth, constipation, lightheadedness or dizziness, and insomnia.

Guanfacine

In the only double-blind, placebo-controlled, crossover study comparing guanfacine with d-amphetamine in adults (n=17), each subject participated in three randomized treatment periods of 2-week duration, with 4-day washouts between trials.32 The measures used for assessment were the DSM-IV ADHD checklist, the Copeland Symptom checklist, and the Stroop Color Subscale and Color-Word test. The mean daily dose of guanfacine was 1.1 mg (0.25-2.0 mg) and 10.2 mg (2.5-20 mg) for d-amphetamine. Guanfacine and d-amphetamine had similar efficacy, and both significantly reduced ADHD symptoms on the ADHD checklist compared with placebo ($p<.05$). Both drugs significantly improved the Stroop Color subscale ($p<.05$). No differences were seen in the rates of AEs between the three groups.

CONCLUSION

With the increasing recognition of under-diagnosed and under-treated adults with ADHD, there has been an explosion of research and clinical focus on effective methods of identifying these patients. In the past 7 years, more treatment options have become available that are specifically approved by the FDA to treat ADHD in adults, thereby improving daily functioning and

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enhancing quality of life for these patients and their families. With other medications in Phase II and III trials, we can anticipate additional effective agents, which will broaden the pharmacologic armamentarium complemented by proven psychotherapeutic approaches.

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Table 1. Medications currently approved by the FDA for treatment of ADHD in adults, in order of approval27

Formulation	Trade Name (Approval Date)	Available Doses (mg)	Starting Dose for Adults (mg/d)
Atomoxetine HCl Non-stimulant	Strattera (November 2002)	10, 18, 25, 40, 60, 80, and 100	40
Mixed amphetamine salts Extended-release stimulant	Adderall XR (August 2004)	5, 10, 15, 20, 25, and 30	20
Dexmethylphenidate HCl Extended-release stimulant	Focalin XR (May 2005)	5, 10, 15, and 20	10
Lisdexamfetamine dimesylate Long-acting prodrug stimulant	Vyvanse (April 2008)	20, 30, 40, 50, 60, and 70	30
Methylphenidate HCl Osmotic controlled release	Concerta (June 2008)	18, 27, 36, and 54	18 or 36