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Changes and Challenges: Managing ADHD in a Fast-Paced World

Michael J. Manos, PhD

Catherine Tom-Revzon, PharmD

Oscar G. Bukstein, MD, MPH

M. Lynn Crismon, PharmD, FCCP, BCPP

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Editor-in-Chief

Frederic R. Curtiss, PhD, RPh, CEBS
830.935.4319, fcurtiss@amcp.org

Managing Editor

Diane Britton
dbritton@amcp.org

Peer Review Administrator

Jennifer A. Booker, 703.317.0725
jmcpreview@amcp.org

Graphic Designer

Elisabeth Squire
www.leapout.com

November Supplement Editor

Mark Jackson, RPh

Account Manager

Peter Palmer, 856.795.5777, ext. 13
peter@promedgroup.net

Publisher

Judith A. Cahill, CEBS
Executive Director
Academy of Managed Care Pharmacy

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FACULTY

Michael J. Manos, PhD, is head, Section of Behavioral Medicine, Children's Hospital, Cleveland Clinic, Ohio. He is also the founding clinical and program director of the Cleveland Clinic's pediatric and adult ADHD Center for Evaluation and Treatment. He is on the medical staff of the Cleveland Clinic Children's Hospital for Rehabilitation and is an adjunct faculty member, Department of Psychology, at both Case Western Reserve University School of Medicine and John Carroll University in Cleveland.

Manos has worked for more than 20 years in pediatric psychology, special education, and child and adolescent psychiatry. He has authored or contributed to numerous articles and book chapters on attention-deficit/hyperactivity disorder (ADHD).

Catherine Tom-Revzon, PharmD, is an associate professor of pharmacy practice, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, and clinical pharmacy manager in pediatrics, Children's Hospital, Montefiore Medical Center. She is also an adjunct assistant clinical professor, Columbia University School of Nursing.

Tom-Revzon is an active member of the Pediatric Pharmacy Advocacy Group and chairs the advocacy committee that focuses on medication safety in children. She has authored manuscripts for pharmacists on ADHD and on psychotropic medication use in children. Tom-Revzon has appeared in various popular media outlets, including *Reader's Digest* and *Child* magazines.

Oscar G. Bukstein, MD, MPH, is an associate professor of psychiatry, University of Pittsburgh School of Medicine. Board certified in psychiatry, child and adolescent psychiatry, and addiction psychiatry, he has substantial research experience in the psychiatric care of children and adolescents, as well as broad experience as a practicing psychiatrist.

Bukstein is currently principal investigator or coinvestigator on several pharmacologic trials for adolescents with substance use disorders, depression, and ADHD. He was primary author of the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter for the Assessment and Treatment of Adolescent Substance Use Disorders (AACAP, 1997).

M. Lynn Crismon, PharmD, FCCP, BCPP, is Dean, Doluisio Chair, and Behrens Inc. Centennial Professor in Pharmacy, University of Texas at Austin College of Pharmacy. In addition, he serves as a clinical psychopharmacologist, Texas Department of State Health Services. He is a member of the faculty and coordinates the clinical psychopharmacology course for the psychiatry residency program, Austin Medical Education Programs, Seton Health Network.

Crismon served as codirector of the Texas Medication Algorithm Project and as director of the Children's Medication Algorithm Project. In collaboration with Rutgers University, he is a coinvestigator on the first mental health Center for Education and Research on Therapeutics, funded by the Agency for Healthcare Research and Quality. He served as associate editor of the *APhA Drug Treatment Protocols*, 2nd edition, as a member of the editorial advisory boards for *The Annals of Pharmacotherapy* and the *APhA DrugInfoLine*, and is a reviewer for numerous journals.

Crismon has served as a member of the Board of Regents for the American College of Clinical Pharmacy (ACCP) and is currently an ACCP fellow.

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*Michael J. Manos, PhD; Catherine Tom-Revzon, PharmD; Oscar G. Bukstein, MD, MPH;
and M. Lynn Crismon, PharmD, FCCP, BCPP*

S14 Continuing Education*: CE Submission Instructions and Posttest Worksheet

Purpose

Provide the most recent information on therapeutic options for ADHD

Target Audience

Managed care pharmacists, pharmacy students, pharmacy technicians, and other interested health care professionals

Learning Objectives

On completion of this activity, participants will be better able to

1. discuss the anatomic sites and neurotransmitter actions thought to be involved in attention-deficit/hyperactivity disorder (ADHD);
2. relate the most common psychiatric comorbidities of ADHD and discuss appropriate treatment for patients with ADHD and comorbidities;
3. describe current therapy formulations and routes of administration and their potential role in reducing abuse liability;
4. describe a clinical management tool for improving patient outcomes in ADHD; and
5. analyze current drug safety issues related to ADHD treatment.

We gratefully acknowledge Shire Pharmaceuticals Inc. for providing an educational grant for this activity.

*This program is approved for 0.2 CEU (2.0 contact hours) (ACPE #073-999-07-077-H01). Pharmacists will be required to complete a posttest and program evaluation. For accreditation information, please see page S14.

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Changes and Challenges: Managing ADHD in a Fast-Paced World

Michael J. Manos, PhD; Catherine Tom-Revzon, PharmD; Oscar G. Bukstein, MD, MPH;
and M. Lynn Crismon, PharmD, FCCP, BCPP

ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) impairs the lives of both children and adults. Undiagnosed and untreated, ADHD may have serious lifelong consequences. Research has identified diagnostic clues, neurotransmitter pathways, and psychiatric comorbidities related to ADHD, as well as effective pharmacologic, behavioral, and psychosocial interventions. Stimulant agents have been the foundation of ADHD therapy for more than 50 years. Availability of new extended-release (XR or ER) and longer-acting (LA) formulations and novel agents allows for wider and more individualized treatment choices. Side effects of stimulants are generally mild, short lived, and responsive to adjustments in dosage or timing. Outcomes in ADHD treatment can be improved with the use of clear treatment guidelines and tools to aid clinicians in implementing them efficiently and effectively. The Texas Children's Medication Algorithm Project (CMAP) provides a system of algorithm-driven treatment decisions that is evidence based and easy to implement.

OBJECTIVE: To (1) review the psychological components of attention, the neurotransmitter pathways associated with ADHD, and the array of therapeutic options for ADHD, with an emphasis on the most recent introductions to the therapeutic armamentarium; (2) discuss the rare psychiatric and cardiovascular side effects associated with stimulants; (3) review abuse liability, comorbidities, and suggested approaches to these issues; and (4) review the development and use of CMAP and offer resources for its implementation in clinical practice.

CONCLUSION: The pathophysiology of ADHD is linked to dysfunction of fronto-subcortical networks and dysregulation of dopaminergic, noradrenergic, and nicotinic neurotransmitter systems. An additive effect of multiple genes as well as environmental influences contributes to the clinical picture. Treatment with stimulants and nonstimulants has proven effective in different subgroups, with the effectiveness of specific agents most likely related to the primary neurotransmitter involved. Availability of XR, ER, LA, and transdermal stimulant formulations, as well as alternative nonstimulant agents, offers new options for the pharmacotherapy of ADHD. Major concerns associated with abuse liability of stimulants have been allayed by the availability of ER formulations, which have reduced reinforcing effects associated with short-acting preparations. Medication outcomes in ADHD can be enhanced by the use of evidence-based algorithms such as CMAP. Keys to success are adequate initial assessment and diagnosis, the use of sustained-release products, sufficient dose titration, and the use of clinical rating scales with feedback from caregivers and teachers. Optimal treatment outcomes can be achieved by appropriate pharmacotherapy combined with psychosocial interventions.

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The psychologist William James defined attention more than 100 years ago as “the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought.... It implies withdrawal from some things in order to deal effectively with others.”¹ Modern psychology has since identified the elements of attention and, by extension, potential areas of impairment in the lives of individuals with attentional dysfunction.

More recently, we have identified the brain anatomy and physiology associated with attention and its dysfunction. The dorsolateral prefrontal cortex is the center of directed attention or executive control as well as of the ability to manage emotion or delay emotional reaction.^{2,3} Signals from the frontal cortex to other parts of the brain direct the accomplishment of a task.

If the signal transmitted by neurotransmitter pathways is weak, attention is drawn to something more interesting. In patients with significant impairment (e.g., attention-deficit/hyperactivity disorder [ADHD]), medication strengthens the signal, allowing the individual to self-direct.

Table 1 lists the respective roles of dopamine and norepinephrine in neurotransmission.⁴ Dopamine improves attention and helps to sustain focus. Norepinephrine increases inhibition of impulsive actions and dampens “noise” (shifting attention, distractibility). Medications such as methylphenidate (MPH), a stimulant, tend to work primarily on dopaminergic pathways; nonstimulants such as atomoxetine tend to affect noradrenergic pathways; and d-amphetamine (AMP) tends to influence both neuromodulatory pathways. The relative impact of stimulant and nonstimulant medicines on these neuromodulatory pathways is not well understood, however.

Authors

MICHAEL J. MANOS, PhD, is head, Section of Behavioral Medicine, Children's Hospital, Cleveland Clinic, Ohio, and founding clinical and program director of the Cleveland Clinic's pediatric and adult ADHD Center for Evaluation and Treatment; CATHERINE TOM-REVZON, PharmD, is an associate professor of pharmacy practice, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, and clinical pharmacy manager in pediatrics, Children's Hospital at Montefiore Medical Center; OSCAR G. BUKSTEIN, MD, MPH, is an associate professor of psychiatry, University of Pittsburgh School of Medicine; and M. LYNN CRISMON, PharmD, FCCP, BCPP, is Dean, Doluisio Chair, and Behrens Inc. Centennial Professor in Pharmacy, University of Texas at Austin College of Pharmacy.

AUTHOR CORRESPONDENCE: Michael J. Manos, PhD, Section Head, Pediatric Behavioral Medicine, Children's Hospital, 9500 Euclid Ave., Desk A120, Cleveland, OH 44195. Tel.: 216.445.7574; Fax.: 216.445.7792; E-mail: manosm@ccf.org

TABLE 1 Catecholaminergic Neurotransmission Relative to ADHD

Dopamine	Norepinephrine
<p>Improves attention</p> <ul style="list-style-type: none"> • Focus • Vigilance • Acquisition • On-task behavior • Perception (?) <p>Enhances signal</p> <p>Striatal – prefrontal</p>	<p>Increases inhibition</p> <ul style="list-style-type: none"> • Behavioral • Cognitive • Motoric <p>Dampens noise</p> <ul style="list-style-type: none"> • Distractibility • Shifting <p>Executive operations</p> <p>Prefrontal</p>

*Adapted from Solanto MV, Arnsten AF, Castellanos FX, eds. (2001).⁴
ADHD = attention-deficit/hyperactivity disorder.

Attention and Impairment

Physiological impairment in individuals with ADHD makes it difficult to carry out the functions of attention (e.g., knowing where to direct attention, filtering out competing stimuli, focusing attention long enough to complete a task, shifting attention appropriately, and inhibiting distractibility and impulsivity).⁵ In addition, children with ADHD experience frequent negative responses to their behavior from adult authority figures. Eventually they associate academic tasks with punishment or criticism, thus compounding their frustration. As a result, academic impairment is often the first negative result of untreated ADHD.

A marked deficit in many children with ADHD is the absence of self-efficacy (people's belief that they are competent to effectively act on the environment to change their circumstances). Other behavioral realms also become a challenge for these children. Ongoing development of a healthy social support network, a positive school attitude, and age-appropriate emotional adaptability gradually deteriorate between ages 7 and 15 years to a greater degree in those with combined-type ADHD (hyperactive/impulsive) than in patients with the inattentive subtype.⁶ Other progressively more harmful impairments ensue in multiple areas of life as the person with untreated ADHD grows into adulthood.

Comorbidities of ADHD

Comorbid conditions often complicate the patient's ability to function and the clinician's ability to diagnose and treat.⁷ The clustering of comorbidities is different in pediatric patients than in adults. Oppositional defiant disorder (ODD), for example, is common in children with ADHD and increases the risk of later substance use disorder (SUD).⁸ Both ODD and conduct disorder (CD) are associated with serious impairment in psychosocial functioning, academic underachievement, and early onset of aggressive

behavior. Aggression, in turn, predicts tobacco smoking, marijuana use, and the severity of SUD.^{8,9}

Generally speaking, externalizing comorbid disorders such as ODD and CD are seen more often in boys, whereas girls tend toward internalizing disorders such as depression and anxiety.¹⁰ However, data on comorbidity in girls may be skewed by the preponderance of ADHD research focusing on boys. Also, girls are twice as likely as boys to have the inattentive type of ADHD and are referred less often because they are less troublesome in school.¹¹ A survey study found ADHD a more serious risk factor for SUD in females than in males.¹¹ In addition, prospective data from a 5-year study suggest that the magnitude of increased risk in girls with ADHD is greatest for major depression and ODD, followed by SUD and anxiety disorders.¹²

Among adults with ADHD, the National Comorbidity Survey Replication reported social phobias as the most common comorbidity (29%, compared with approximately 8% in adults without ADHD). Other prevalent comorbidities reported in adults with ADHD compared with adults without the disorder include bipolar disorder (19% vs. 3%); major depressive disorder (18% vs. 8%); and alcohol dependence (6% vs. 2%).¹³

Using Family Context in Diagnosis

Environmental risk factors can be helpful in diagnosing ADHD and comorbidities. Biederman and colleagues demonstrated a positive association between Rutter's adversity indicators¹⁴ and the risk for ADHD and its associated psychiatric, cognitive, and psychosocial impairments.¹⁵ The risk increased with a higher number of adverse environmental factors, which include severe marital discord, low social class, large family size, paternal criminality, maternal mental health disorder, and foster care placement. Boys had a higher risk than girls for adverse cognitive and interpersonal outcomes such as learning disability and impaired scores on the Global Assessment of Functioning Scale.¹⁶

Treating ADHD and Comorbidities

Treating externalizing disorders usually requires medication, which may also improve the symptoms of ODD and CD and which, in turn, can improve development of the child's social network.⁷ Despite the commonly held notion that psychostimulant treatment increases risk for developing SUD, particularly in youth with comorbid ODD or CD, a meta-analysis of published studies led to the opposite conclusion: treating ADHD during childhood reduces the incidence of SUD by half, while failure to treat doubles the risk for SUD.¹⁷ These data are not meant to suggest that all children with untreated ADHD will eventually develop SUD, but rather that the probabilities favor pharmacotherapy.

Medications Approved by the Food and Drug Administration (FDA) for ADHD

The optimal approach to treatment of ADHD combines medication and behavioral intervention.^{18,19} A variety of stimulants and

TABLE 2 Effect Sizes*

(29 controlled studies, 4,465 children and adolescents)

Drug	Effect Size
Amphetamine	0.92
Methylphenidate	0.80
Atomoxetine	0.73
Modafinil	0.49
Bupropion	0.32

*Drugs used to treat ADHD were evaluated for efficacy using 17 outcome measures. Effect sizes for stimulants (amphetamine and methylphenidate) are significantly greater than those for other medications.
Data from Faraone SV and Spencer TJ (2006).²²

TABLE 3

Treatment Trend: Extended Duration of Action

Medium-acting (about 8 hours)*

- Extended-release methylphenidate
- Long-acting methylphenidate

Long-acting (10-12 hours)

- Extended-release dexamethylphenidate
- Mixed amphetamine salts extended-release (MAS XR)
- OROS methylphenidate
- Lisdexamfetamine

Longer-acting (16 hours)[†]

- Mixed amphetamine salts, triple-bead formulation
 - Investigational for adult ADHD; NDA submitted in 2006
 - Bioequivalent to MAS XR followed by MAS IR 8 hours later[‡]

*Connor DF, Steingard RJ (2004).²⁴

†Grcevich S. (2006).²⁵

‡Youcha SH et al. (2006).²⁶

ADHD=attention-deficit/hyperactivity disorder; IR=immediate release; MAS=mixed amphetamine salts; NDA=New Drug Application; OROS=osmotically controlled-release oral delivery system; XR=extended release.

nonstimulant medications feature a widening array of delivery systems. The safety and efficacy of the stimulants MPH and AMP have been established by more than 50 years of research and clinical use.^{20,21}

Effect Sizes and Response to Medications

A recent meta-analysis of 29 double-blind placebo-controlled studies over the past 25 years indicates that stimulants tend to be more effective than nonstimulants in treating ADHD in pediatric patients (Table 2).²² The studies enrolled a total of nearly 4,500 children and adolescents aged 8 to 15 years. Pharmacologic response rates for the stimulant class track as robust in this analysis.²³

Treatment Trend: Extended Duration of Action

Current thinking in ADHD therapy focuses on assessing duration of action and determining which delivery system is appropriate for the patient. Table 3 lists the stimulant agents according to medium-, long-, and longer-acting (LA) duration of action.²⁴⁻²⁶ The longest-acting agent is SPD465, a triple-bead formulation of mixed amphetamine salts (MAS) that in May 2007 received an FDA-approvable letter for adults with ADHD. In a phase 1 trial, SPD465 at 37.5 mg was bioequivalent to MAS XR (extended release) 25 mg plus MAS IR (immediate release) 12.5 mg given 8 hours later.

Treatment Trend: Novel Delivery Systems

Novel delivery systems, some of which have been available for several years, further help to individualize treatment. In the Diffucaps® MPH (Metadate) system, the beaded preparation is released biphasically—30% of the dose immediately and 70% as extended release. A 20 mg dose is equivalent to 6 mg initially and 14 mg 4 hours later.²⁷ Contents of the capsule may be sprinkled on applesauce for ease of dosing younger patients.

The spheroidal oral drug absorption system (SODAS), exemplified by MPH LA (Ritalin LA), has an IR bead that releases half the total dose and an enteric-coated, delayed-release (DR) bead that delivers the remaining drug 4 hours later.²⁸ Dexamethylphenidate (Focalin, d-MPH XR) is a d-threo enantiomer of racemic methylphenidate hydrochloride packaged in a capsule that also uses SODAS technology.²⁹ MPH SR (Ritalin sustained release) uses a simpler, wax-based delivery system designed for slow release of 5 to 8 hours. However, drug release has reportedly been unacceptably variable.³⁰

The osmotically controlled-release oral delivery system (OROS) for MPH (Concerta) contains an IR component in the outer covering and a progressive, 8-hour release of the remaining drug through the osmotic pump. An 18 mg dose delivers about 4 mg initially and the remainder over the next 8 hours.³¹

MAS XR (Adderall XR) tablets contain 3 types of d-AMP and 1 type of l-AMP and provide an extended duration of action for 12 hours via IR and DR beads.³²

All the delayed delivery systems decrease the abuse potential of the stimulant agents. Another way to reduce abuse potential is to completely change the delivery system. Transdermal MPH (Daytrana) was approved in 2006 for use in children aged 6 to 12 years.³³ When the patch is left on for 9 hours, the duration of action is about 12 hours. However, dosing is flexible: the hours of coverage can be regulated by leaving the patch on or taking it off.

For pharmacists in health system locations that may not carry all the different formulations for ADHD treatment, it is important to note that the dosage conversion from 1 long-acting product to an IR product or another dosage form of the same active drug is not necessarily 1:1. For example, a patient who was taking OROS MPH 18 mg once daily can be switched to MPH IR 5 mg 2-3 times a day.

■ Treatment Trend: Prodrug With Reduced Abuse Potential

Lisdexamfetamine dimesylate (Vyvanse, LDX), which was FDA-approved for marketing in February 2007, is an AMP prodrug that is inactive until metabolized.³⁴⁻³⁶ The drug molecule is a prodrug as it is covalently bound to l-lysine, an amino acid; after ingestion, hydrolysis releases the d-AMP gradually. LDX doses of 30, 50, and 70 mg are equivalent to 10, 20, and 30 mg doses of MAS XR in terms of efficacy and duration of action (12 hours).³⁷

The prodrug attenuates the onset and intensity of AMP-like effects and is less reinforcing than equivalent doses of d-AMP, contributing to a lower abuse potential. In adult stimulant abusers, LDX had a later peak effect and was less euphoric than comparable doses of d-AMP.³⁴ Intravenous LDX was significantly less reinforcing than d-AMP; the majority of subjects chose not to take LDX again. In terms of "likeability," 50 or 100 mg of LDX was similar to placebo, and 150 mg LDX (much higher than doses recommended for clinical use) was similar to d-AMP but with a delayed peak effect. LDX is classified as a schedule II controlled substance.³⁸

■ Strategies for Stimulant Titration

Guidelines for titrating stimulant medication generally endorse a "start low and go slow" approach. Practice parameters from the American Academy of Child and Adolescent Psychiatry provide clear guidelines.³⁹ In general, physicians use 3 approaches in titration:

1. Prescribe and wait.
2. Gradually increase dose until behavior improves.
3. Ramp up until side effects appear, then reduce dose to the level before they appeared.

Management of side effects depends on severity. Mild appetite suppression and/or insomnia are usually expected and tolerable; however, if these side effects rise to the moderate level, the dose should be decreased. Severe side effects warrant discontinuing the medication or trying a different one.³⁹

It is critical during the titration process to have reliable information about the child's behavior from multiple sources, particularly teachers, who are with children for the majority of the day during the school year. However, 1 survey found that only 3% of teachers were asked to report their observations to a clinician while a child's medication was being titrated.⁴⁰

■ Approved Nonstimulant Medication: Atomoxetine

Atomoxetine (Strattera), a selective norepinephrine reuptake inhibitor in the presynaptic neuron, also has some effect on dopamine inhibition in the frontal lobes.⁴¹ The only nonstimulant currently FDA-approved for ADHD in children, adolescents, and adults, atomoxetine has shown efficacy in more than 10 controlled trials.⁴² (Recent studies show effectiveness and tolerability of 2 years' therapy in young children⁴³ and adolescents.⁴⁴) Atomoxetine is unscheduled (no addictive liability) and prescriptions are renewable; however, the product carries a black box warning regarding suicidal ideation.⁴¹ The average risk of suicidal ideation, based on

11 ADHD trials, was 0.4% (5/1,357 patients) compared with no risk in placebo-treated patients. The labeling indicates the risk of suicidal ideation is greater early in the course of treatment.

Another change in labeling pertains to rare cases of severe liver injury from postmarketing reports in 2 adult patients involving jaundice and elevated hepatic enzymes 40 times the upper limit of normal. Recovery from the hepatic injury occurred after discontinuation of atomoxetine, and neither patient required a liver transplant. Patients should be educated about signs of liver dysfunction (pruritus, dark urine, jaundice, right upper-quadrant tenderness, or unexplained "flu-like" symptoms) so that prompt medical care can be sought.⁴¹

■ Adjunctive or Alternative Treatment

Additional or adjunctive therapy with nonstimulants (other than atomoxetine) is recommended if the patient fails to respond to trials of 2 different stimulants (MPH and AMP), has intolerable side effects with stimulants, or fails to respond to a trial of atomoxetine. Options for second-line agents include antidepressants such as bupropion, tricyclic antidepressants, or venlafaxine. Some data show positive neuropsychological effects of nicotinic modulators.⁴⁵ Other potentially useful agents include cholinesterase inhibitors, noradrenergic/dopaminergic agonists, and alpha-2a-adrenoreceptor agonists such as clonidine and guanfacine.^{46,47}

■ Emerging Treatment: New Nonstimulant Formulation

An ER form of guanfacine (a selective alpha-2a-adrenoreceptor agonist currently indicated for the treatment of hypertension) has been studied for ADHD treatment in children aged 6 to 17 years. In a phase 2 trial, guanfacine ER monotherapy in once-daily doses of 1 to 4 mg produced significantly improved control of ADHD symptoms versus the placebo group.⁴⁸ An ongoing phase 3b controlled trial is studying flexible dosing of the agent in 6- to 12-year-olds with ADHD and oppositional behavior.⁴⁹ Study completion is expected in January 2008.

■ Wakefulness Agent: Modafinil

Modafinil is currently approved for the treatment of narcolepsy and excessive daytime sleepiness,⁵⁰ but its mechanism of action is not precisely known. Modafinil is not a dopamine receptor agonist but according to the prescribing information, its wakefulness-promoting actions resemble those of AMPs and MPH.⁵¹ Recent data examining modafinil in ADHD have been reasonably robust. Positive results were seen in 2 randomized controlled trials in children aged 6 to 13 years and 6 to 17 years, respectively.⁴⁷ Abrupt discontinuation did not induce withdrawal symptoms or rebound.⁵¹ Modafinil is classified as a schedule IV controlled substance.

However, the FDA Pediatric Advisory Committee in March 2006 questioned the safety of modafinil for pediatric patients because of concerns over the possible development of Stevens-Johnson syndrome. In August 2006 the FDA declined to approve modafinil for pediatric ADHD pending further safety evaluations.⁵²

■ Unproven Treatments

Data are still lacking to support a notable benefit of most alternative approaches in ADHD. Such unsubstantiated approaches include electroencephalography biofeedback training, megavitamin therapy, herbal treatments, body and craniosacral manipulation, sensory integrative training, and specific supplements.^{53,54} A small percentage of children with ADHD may have particular sensitivities to foods or additives; elimination diets may help to identify these patients. In a small placebo-controlled crossover study comparing an oligoantigenic diet (eliminating common allergenic foods) with stimulant treatment, 24% of children in the diet group and 44% in the stimulants group showed significant behavioral improvement.⁵⁵ This study showed minimal clinical improvement with the diet in comparison with the medical approach.

■ The Multimodal Treatment Study of ADHD

The Multimodal Treatment Study of ADHD (MTA) established that combination behavioral therapy and pharmacotherapy improves overall outcomes in children with ADHD.⁵⁶ This multi-site National Institute of Mental Health (NIMH) study included 579 children aged 7 years to 9.9 years who were assigned to 4 treatment groups: (1) state-of-the-art medication; (2) intensive behavioral intervention; (3) combination medication and behavioral intervention; and (4) community treatment (usual care).⁵⁷

Comorbid anxiety disorders responded equally well to combination treatment or medication alone. However, in the group with ADHD and comorbid anxiety, behavioral therapy was equal to medication for some symptoms, particularly in the smaller group without CD. In the group with ADHD only or ADHD plus ODD or CD, improvement required medication treatment, and there was no added benefit from the behavioral treatment.⁵⁸

■ Safety in Young ADHD Patients

The NIMH-sponsored Preschool ADHD Treatment Study (PATS), published in 2006, reported a marked decrease in ADHD symptoms in 3 to 5.5-year-old patients with symptoms of severe ADHD who received MPH doses of 2.5 mg, 5.0 mg, and 7.5 mg administered thrice daily, as compared with placebo. In this dose titration study, the mean optimal total daily dose for the MPH group was approximately 14 mg+8.1 mg (0.7 mg+0.4 mg per kg per day).⁵⁹ MPH doses were tolerated by 92% of 183 patients in the treatment group during a 1-week open safety lead-in phase.⁶⁰ The 165 patients randomized to MPH in the 5-week, placebo-controlled, double-blind phase of the study had smaller effect sizes (0.4 to 0.8) than did school-age children in the MTA study. Side effects, such as appetite loss, trouble sleeping, stomach aches, social withdrawal, and lethargy, were reported more often with the high MPH doses across the study. The overall rate of treatment discontinuation was 11% due to moderate or severe side effects, primarily emotionality and irritability. No episodes of mania or suicidality were reported. No cardiovascular side effects required follow-up.⁶⁰ Growth rates were lower than expected for height and weight in this

segment of the study,⁶¹ and investigators plan a 5-year follow-up study to examine the risk-benefit effects of treatment as children age.

■ Psychosocial Interventions in ADHD

Changing the environment around the child and altering the expectations for performance is more effective than is an approach that makes the person “wrong,” places the pathology solely in the child, and attempts to change or “fix” the child to the exclusion of other influencing factors. To successfully manage directed attention, the child needs immediate feedback for accomplishment of one task, followed by immediate introduction to the next task. Task orientation, for example, can be simplified by breaking large tasks into small tasks and breaking work periods into smaller intervals. Parents and teachers should (1) use a combination of positive and negative contingencies, not just aversive consequences, to promote academic skills, wellness, and positive social behavior; (2) avoid long discussions about appropriate behavior; (3) give themselves frequent feedback on how effective they are being with the child; and (4) maintain a consistent daily routine.

A small but growing body of literature is validating the efficacy of psychosocial interventions in ADHD therapy. Some issues, such as the optimal duration of therapy, remain to be determined. In children, play therapy, behavioral modification and coaching, and parent training are under study.⁶² For adolescents, success has been reported with behavior techniques, academic interventions, family therapy, and integrating or coordinating various aspects of care.²¹ Individual therapy is successful with comorbidities.⁶²

Adults may respond to cognitive-behavioral therapy, which includes enhanced organizational and planning skills, problem-solving skills, reduction of distractibility, and elimination of dysfunctional thoughts.⁶³

For most patients, psychosocial treatment plus medication is optimal, but ultimately an individualized treatment plan is needed for each patient.

■ Improving Adherence

Adherence to ADHD medication regimens decreases significantly over time. In 1 review, nearly half of children aged 9 years to 15 years stopped taking their ADHD medication over a 3-year period.⁶⁴

Several strategies have been effective for improving adherence^{21,64-66}:

- Educate patients and parents about anticipated results, benefits, and possible adverse effects.
- Provide frequent follow-up early in treatment, especially during dose titration.
- Strive for dose optimization.
- Identify and treat comorbid conditions.
- Equip parents to answer inevitable questions from friends and relatives.
- Use extended-release formulations, transdermal delivery, and school accommodation plans.

A 12-month study examined medical claims data for more than

16,000 patients aged ≥ 6 years who were newly diagnosed with ADHD and had been started on a 30-day prescription.⁶⁴ Over that year, patients who saw their physicians more frequently tended to fill more prescriptions for ADHD medications. Adherence ratios ranged from about 38% (associated with only 1 to 2 office visits) to 70% (11 office visits). Clearly, keeping in touch with patients improves adherence.

■ Changes and Challenges

Although hundreds of studies have demonstrated the efficacy and safety of stimulants in ADHD treatment, these agents, like most medications, are not risk free. However, side effects—most commonly, insomnia and loss of appetite—are generally mild, short lived, and responsive to adjustments in dosage or timing.^{39,67} The FDA has recently issued statements on several rare side effects related to cardiovascular and psychiatric systems. Tic disorders and the rates of growth in younger patients have also gained attention as potential concerns. The FDA has directed manufacturers of ADHD drugs to develop Patient Medication Guides regarding possible cardiovascular and psychiatric risks and to explain precautions that can be taken.⁶⁸ The FDA's online notice includes a link for a list of draft Medication Guides, some of which have been incorporated in updated product labeling.⁶⁹ Following is a brief discussion of published data and recommendations to clinicians regarding these issues.

Cardiovascular Events

In recent years, concern has focused on reports of cardiovascular events in a very small percentage of patients.⁷⁰ The incidence of sudden death associated with ADHD medications (12 cases between 1999 and 2003) is markedly lower than the base rate of sudden death expected in children <18 years.^{70,71}

- Sudden death associated with ADHD medications: 0.2-0.05 per 100,000 patient-years⁷⁰
- Sudden death expected in all patients $<age 18$: 1.3-8.5 per 100,000 patient-years⁷¹

These data suggest that the general risk for sudden death in those prescribed stimulants is within, if not lower than, the range of sudden death in the general population. In a review of stimulant-related cases of sudden death, the FDA identified possible risk factors for severe cardiovascular events, including preexisting heart disease or symptoms suggesting significant cardiovascular disease (history of severe palpitations, fainting, exercise intolerance not related to obesity, or strong family history of sudden death); structural abnormalities (tetralogy of Fallot, coronary artery abnormalities, subaortic stenosis); and significant signs or symptoms such as chest pain, arrhythmias, hypertension, or syncope (which may be signs of hypertrophic cardiomyopathy). If any such issues are present, consultation with a cardiologist is advised. There is no evidence of a need for routine cardiac evaluation such as electrocardiogram before stimulant treatment in otherwise healthy individuals.^{72,73}

In March 2006, an FDA Pediatric Advisory Committee unanimously declined to recommend a black box warning about cardiovascular events in labeling for stimulant medications. Rather, the committee asked that labeling highlight the risk in children with underlying cardiovascular pathology.⁷⁴

Psychiatric Side Effect Potential

Many individuals with ADHD also have aggressive behavior, which tends to decline when they are treated with stimulants.⁷⁵ Baseline behavior and symptoms should be assessed before treatment. In controlled studies, the differences in aggressive behavior between active treatment and placebo did not reach statistical significance.⁷⁵ Rare reports of toxic psychotic symptoms (visual and tactile hallucinations of insects) have been associated with all stimulants as well as with atomoxetine and modafinil in therapeutic doses.

For other rare or infrequent occurrences, including psychosis or mania or new onset or severe exacerbation of aggression, physicians should stop the medication and assess the risks and benefits of treatment. The FDA advisory committee noted the importance of using patient information sheets to communicate with patients and parents about these rare risks. The FDA recommended labeling changes, noting that aggression can be part of ADHD and can be decreased with stimulant treatment, and that new episodes or exacerbation of aggression should be discussed with the doctor, who should consider stopping the medication.⁷⁴

Medication and Growth

The jury is still out with regard to the effects of ADHD medication on growth. A review of studies found a reduction in growth compared with expected height gain, at least during the first 2 years of therapy. The height deficit amounted to approximately 1 cm per year during the first 1-3 years of treatment.⁷⁶ However, subsequent data show that therapy does not slow the rate of height acquisition below the mean expected height for age.⁷⁷ Clinical experience suggests that in most children who are treated, the slower growth rate seen early in therapy attenuates and ultimately disappears, resolving by adulthood, although the deficits seen in the first several years (approximately 2.5 cm [1 inch]) may persist.^{78,79}

Medication and Tics

The original basis for warnings against using stimulants in children with tics was based on anecdotal clinical observations. Since then, a group of well-controlled studies has reported that MPH and d-AMP are effective, well tolerated, and safe in children with tics.^{80,81} On average, tics improve rather than deteriorate when exposed to stimulant medication.⁸⁰ However, if tics occur or worsen during a trial of stimulants, an alternative stimulant or a nonstimulant such as atomoxetine should be tried.⁸² Combined therapy with an alpha-agonist or antipsychotic agent is often effective and safe in children whose ADHD symptoms respond only to a tic-inducing stimulant.⁸³

Stimulant Abuse, Misuse, and Diversion Liability

The terms *abuse*, *misuse*, and *diversion* have different definitions, which need to be understood to appreciate the diverse risk of prescribed medications for ADHD:

Abuse. Recurrent use with problems relating to hazardous situations, legal difficulties, fulfillment of major obligations, social or interpersonal problems.⁸⁴ Abuse is a DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*) term defining a pathology of repeated substance use with negative consequences.

Misuse. Use for a purpose that is not consistent with medical guidelines (e.g., modifying dose, using to achieve euphoria, using with other nonprescribed psychoactive substances to enhance the reinforcing effect).⁸⁵

Diversion. Transfer of medication from the individual for whom it was prescribed to one for whom it is not prescribed.⁸⁵ This can occur within a child's household, when a child or adolescent "shares" medication or sells it to peers, or when another person steals the medication, a not-uncommon scenario on college campuses.

Diversion and Misuse: Short Acting Only

The authors of a 10-year longitudinal study of youths with ADHD evaluated medication diversion or misuse at the last follow-up period. They found that 22% of young adults with ADHD misused their medication and 11% diverted it.⁸⁵ Importantly, only short-acting stimulants were misused or sold, and all those responsible had a history of CD or SUD.

The misuse of stimulants as "study drugs" is not uncommon on college campuses.⁸⁶ A recent Web-based survey found a past-year prevalence of 6% of 4,580 college students reporting stimulant misuse (75% used AMPs, 25% MPH), with a lifetime prevalence of 8%.⁸⁷ A survey of 11,000 college students at 119 institutions calculated 4% past-year prevalence for nonmedical use of prescription stimulants (7% lifetime).⁸⁸

Most undergraduates (60%) of the misusing cohort at 1 college (prevalence: 5.4% of 9,000 surveyed) reported that stimulants "help me concentrate"; 40% said stimulant use "helps increase my awareness." However, another 40% also reported that use of IR stimulants "gives me a high."⁸⁹ This group is at risk for developing stimulant abuse or dependence, and there are red flags that may help to identify them.

Red Flags for Diversion or Misuse

Several behaviors may indicate misuse or diversion:

1. *Continuously escalating doses.* Tolerance may be an issue with some patients, but dose escalation tends to be rapid in those misusing the medication.
2. *The infrequent user who comes in every 6 months for a 1-month prescription.* One has to wonder what that patient is doing with the medication.
3. *Increased symptoms of psychosis.* With excessive doses, the risk of developing psychotic symptoms, particularly hallucinations,

increases.

4. *Palpitations, syncope, shortness of breath.* Cardiac symptoms that are a risk at supratherapeutic doses can increase.
5. *Repeated discordant pill counts or lost prescriptions.* A patient repeatedly comes in too early for a new prescription.
6. *Patients calling for an "emergency supply."*
7. *Demands for immediate-release stimulants.*
8. *Signs of substance abuse.* The patient may have developed an SUD.

Factors Influencing Abuse Liability

Drugs that have reinforcing effects or are formulated for quick delivery to the brain have more appeal to substance abusers. Delivery systems, routes of administration, and drug formulations all influence the abuse liability of therapeutic agents for ADHD. The current availability of agents and delivery systems that discourage reinforcing effects is expected to significantly diminish the abuse liability of stimulants.

SUD in ADHD: Clinical Considerations

In considering the comorbidities of ADHD and SUD, the clinical rule of thumb is to treat the disorder that will have the most immediate effect on outcome—the problem that is the most impairing and is, perhaps, an obstacle to treatment of the other problem. Generally, in adults with ADHD, "the other disorder" is treated first, particularly if the comorbidity is SUD. Substance abstinence or reduced use may be necessary before a diagnosis is made, and the patient should be well engaged in treatment before medication trials, particularly stimulants, are considered.

Assessing patients with SUD requires several clinical considerations to determine the level of risk:

- Did the SUD occur in the past and is not ongoing? If so, the concern level is lower.
- What specific substance is involved? The patient who is abusing cocaine or a stimulant is at higher risk. In that case, nonstimulants might be appropriate first-line therapy for ADHD. Precautions with these patients include limiting the number of pills dispensed and monitoring the count, obtaining urine toxicology, and scheduling frequent patient visits.
- Who is responsible for storing and administering the medication? For children or adolescents, parents must take on these responsibilities. Pharmacists should maintain good communication levels with prescribing physicians.

In children, clinicians generally treat the ADHD before treating a comorbid condition. Some data suggest that nonstimulant agents shown to have efficacy in ADHD may also be helpful in treating comorbidities; for example, atomoxetine for comorbid anxiety and bupropion for comorbid depression.⁹⁰ Potential concurrent treatments with stimulants include selective serotonin reuptake inhibitors (SSRIs) and mood stabilizers (particularly in bipolar disorder).

Optimal use of monotherapy is the initial goal, and polypharmacy should be avoided when possible. Clinicians are advised to

carefully evaluate each trial of an added medication, discontinue an ineffective medication, monitor adherence and adverse effects, and remember that psychosocial treatments can boost treatment efficacy in ADHD.

Clinical Tool for Improving Patient Outcomes

One program that has demonstrated improved treatment outcomes in ADHD is the Children's Medication Algorithm Project (CMAP). An initiative of the University of Texas and the Texas Department of State Health Services, CMAP was designed to improve the health outcomes of individuals treated in the public mental health sector. As the most common disorder in children and adolescents within the state mental health system, ADHD was included in the project.⁹¹ A consensus panel reviewed the evidence and issued recommendations. The panel included academic-content experts, practicing clinicians, administrators, consumers, family members, and mental health advocates.⁹²

Components of the Algorithm

Algorithm strategies answer these questions:

- What treatment regimens are acceptable?
- In what order should they be used (for sequential treatment interventions)?
- How does one optimally implement a treatment regimen in an individual patient?
- What is the starting dose?
- What steps should be included in dose titration and at what point?
- What should be the maximum dose?
- What is the basis for evaluation of patient outcomes—decreased symptoms, improved function, or adverse effects?
- How long should treatment continue when it appears to be ineffective?
- What should be the approach for partial responders?
- What is the optimal approach to switching regimens?⁹³

Algorithm for ADHD With No Significant Comorbidities

Stage 0 (before beginning any psychotropic medications) consists of a diagnostic evaluation based on a history and thorough interview with the child, the parent, and, if possible, the child's teacher (Figure). Teachers' impressions are important, as the child's behavior may be totally different at school. Other causes of the behavior should be ruled out. Treatment must be a partnership; the clinician and parents should discuss therapeutic options and stay in contact throughout the course of treatment. Without the family's buy-in, the clinician's treatment decisions will not be effective.

The possible need for behavioral therapy interventions, including family skills training, should be discussed with the family before beginning pharmacotherapy. If possible, tools such as the ADHD Rating Scale, the Vanderbilt Assessment Scale, and SNAP-IV Teacher and Parent Rating Scale should be used to evaluate responses.

FIGURE Algorithm for the Pharmacological Treatment of ADHD (With No Significant Comorbid Disorders), Revised 2005

Pliszka SR et al. (2006).⁴²

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DEX=dextroamphetamine; MAS=mixed amphetamine salts; TCA=tricyclic antidepressants.

Stage 1 is essentially the clinician's choice of a stimulant, either MPH or an AMP product. An SR formulation may be preferred so the child will be spared the embarrassment of taking medication at school, thus improving adherence.⁹⁴

If the patient does poorly clinically or has intolerable adverse effects during stage 1, stage 2 suggests initiating the alternate stimulant choice. It is strongly urged that monotherapy with both types of stimulants be tried before moving to a different drug class. The clinician should even try different formulations of the same chemical entity, particularly if adverse effects complicate treatment or if clinical effect fluctuates throughout the day.

Stimulants are the most rapid acting and predictable treatments available in psychopharmacology; response to stimulants usually occurs within 2 hours.⁴² Given that variable stresses and strains may occur on any given day, it is necessary to evaluate the child over the course of several days to assess overall response to the medication. As with the original assessment, this evaluation of the treatment effect should come from the rating scale, the child, the parent, and the teacher.

Dosing is extremely important. The MTA study showed greater responses on higher than on lower doses⁵⁶ but the optimal dose in a given individual cannot be predicted in advance. The CMAP tactic suggests forced titration at different doses, using a rating scale application at each dose level, and assessing the dosage that best helped the child. The MTA study protocol assessed each of 3 or 4 different doses for 1 week. However, in actual clinical practice, changing doses weekly may be difficult even with the use of convenient rating scales and reporting methods such as telephone, e-mail, and fax.

Both clinicians and parents tend to resist forced dose titration. Parents may be satisfied with initial partial response when their child is doing somewhat better on a lower dose and may resist pushing the dose further. Thus in practical terms, titration may have to occur over a longer period. Pharmacy claims database analyses suggest that it typically takes months for dosage titration to occur (unpublished observation). Annual pharmacy data often show a large peak in numbers of stimulant prescriptions, particularly new starts, near the end of September when the first school report cards of the year are issued.⁹⁴ Unfortunately, with months-long titration to optimal dosage, most of a school year may be lost before the child is adequately dosed.

Up to 80% of patients who receive an adequate therapeutic trial on MPH or MAS will respond to one or the other medication.⁹⁵ For patients who fail to respond after trials of 2 different stimulants, clinicians should first reassess the diagnosis and investigate adherence, adequacy of dosing, potential comorbidities, and the family environment. Family skills training should be initiated or enhanced if it was inadequately implemented when therapy was initiated.

Nonstimulant alternatives have smaller effect sizes than do the stimulants but can be tried in stages 3, 4, and 5 of the algorithm. If treatment at the primary care level has produced an inadequate response, psychiatric evaluation should be considered.

Psychoeducation

Parents of children with ADHD need accurate information about the disease state, treatment options, how treatment is optimized, and myths associated with ADHD. Caregiver resources and support can be made available in group settings using consumer and family facilitators and through reliable Internet sources. Appropriate follow-up, adequate contact, and additional support all help to maintain treatment adherence and increase the chance of success.⁹⁶ In a study of the role of educational services, families were significantly happier with the clinic that provided educational services than with the one that did not (all children received medication treatment).⁹⁷

CMAP: Comorbidities

The CMAP algorithm includes recommendations for treating ADHD associated with comorbidities.⁴² The Web site www.dshs.state.tx.us/mhprograms/adhdpage.shtm provides algorithms for treating ADHD alone and with cooccurring anxiety disorder, major depressive disorder, tic disorder, and aggression. The site also includes tactics tables for the use of stimulants, tricyclic antidepressants, bupropion, alpha-antagonists, and SSRIs.⁹⁸

■ HEDIS Measures for ADHD

The Healthcare Effectiveness Data and Information Set (HEDIS) of the National Committee on Quality Assurance published its first measure for ADHD treatment in 2006.⁹⁹ The measure requires at least 1 follow-up visit with a practitioner with prescriptive authority during the 30-day initiation phase of treatment and at least 2 additional follow-up visits with a practitioner within 9 months after the end of the initiation phase.

However, positive treatment outcomes require more frequent follow-up visits than HEDIS requirements state. These visits need not be with a physician but can be with any health care provider who is knowledgeable about treating ADHD and can apply principles of disease management.

■ Assessing Quality of Life

Care plans for patients with ADHD should always include quality-of-life surveys: AIM-A for adults¹⁰⁰ and AIM-C for children.¹⁰¹ Both assess quality of life for the patient and for the caregiver, usually 1 or both parents. The Child Health Questionnaire is a generic instrument that is also used to assess physical and psychosocial aspects and includes parent sections.^{102,103}

■ Additional Resources

Table 4 lists Web sites of some health plans that offer provider toolkits for optimal management of ADHD and helpful information for consumer psychoeducation. For an overall approach to disease management, medication treatment should be supported by adjunctive psychoeducational programs, ample patient contact, and frequent follow-up visits throughout the course of therapy.

TABLE 4

Managed Care Toolkits for ADHD

- **Health Plan of Michigan** <http://hpmich.com>
- **Neighborhood Health Plan of Rhode Island** <http://www.nhpri.org>
- **PacificCare Behavioral Health** <http://www.pbhi.com>
- **Magellan Behavioral Health** <http://www.magellanprovider.com>

ADHD = attention-deficit/hyperactivity disorder.

Summary: Emerging View of ADHD

The pathophysiology of ADHD is linked to dysfunction of fronto-subcortical networks and dysregulation of dopaminergic, noradrenergic, and nicotinic neurotransmitter systems. An additive effect of multiple genes as well as environmental influences contributes to the clinical picture.

Treatment with stimulants and nonstimulants has proven effective in different subgroups, with the effectiveness of specific agents most likely related to the primary neurotransmitter involved. The availability of XR, ER, LA, prodrug and transdermal stimulant formulations, as well as alternative nonstimulant agents, offers new options for the pharmacotherapy of ADHD. Major concerns associated with the abuse liability of stimulants have been allayed by the availability of the new formulations, which reduce the reinforcing effects associated with short-acting preparations.

Patients and parents should be informed about the low incidence of serious side effects with ADHD treatment. Medication outcomes in ADHD can be enhanced by the use of evidence-based algorithms such as CMAP. The best treatment outcome can be achieved by appropriate dosing and titration as well as by a combination of pharmacotherapy and psychosocial intervention.

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Changes and Challenges: Managing ADHD in a Fast-Paced World

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The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this program, you must complete the following forms online:

1. Posttest form for this program, “Changes and Challenges: Managing ADHD in a Fast-Paced World,” on the AMCP.org Online Learning Center site. To receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form

Upon successful completion of this program, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org Online Learning Center site. All information is kept confidential.

Note: There is a \$10 processing fee for nonmembers. (See payment instructions on site.)

Posttest Worksheet: Changes and Challenges: Managing ADHD in a Fast-Paced World

1. The center of directed attention or executive control, as well as the ability to manage emotion or delay emotional reaction, lies in what area of the brain?
 - a. Dorsolateral prefrontal cortex
 - b. Locus ceruleus
 - c. Substantia nigra
 - d. Medulla
2. Norepinephrine functions in the brain to
 - a. stimulate impulsive actions.
 - b. inhibit impulsive actions.
 - c. increase distractibility.
 - d. inhibit learning.
3. Stimulant medications act on which 1 of the following neurotransmitter pathways?
 - a. Noradrenergic
 - b. Dopaminergic
 - c. Opioid
 - d. GABA
4. Nonstimulant medications act on which neurotransmitter pathways?
 - a. GABA
 - b. Dopaminergic
 - c. Opioid
 - d. Noradrenergic
5. Children and adults with attention-deficit/hyperactivity disorder (ADHD) experience similar psychiatric comorbidities.
 - a. True
 - b. False
6. Comorbid oppositional defiant disorder (ODD) in patients with ADHD often increases the risk of
 - a. substance use disorder (SUD).
 - b. schizophrenia.
 - c. social phobias.
 - d. bipolar disorder.

7. Which of the following statements is false?
 - a. Youths with ADHD and ODD should not be treated with stimulants.
 - b. Pharmacologic treatment of ADHD during childhood reduces the risk of SUD development.
 - c. Failure to treat ADHD during childhood doubled the risk for SUD, according to a recent meta-analysis.
 - d. The fear that stimulant treatment induces SUD is generally unfounded.
8. Current recommendations for medication management of ADHD suggest
 - a. long-term daily use of medication, possibly with extended duration of action to cover a school or work day.
 - b. individualized dose titration.
 - c. an ascending stimulant concentration profile.
 - d. all of the above.
9. Which of the following agents is not formulated to provide all-day coverage?
 - a. OROS methylphenidate (MPH)
 - b. Diffucaps MPH system
 - c. MAS IR
 - d. MPH patch
10. Concerns associated with abuse liability of stimulants have been allayed in part by
 - a. availability of extended-release formulations.
 - b. closer tracking of adolescents with ADHD and comorbid ODD.
 - c. careful avoidance of prescribing stimulants to adolescents with newly diagnosed ADHD.
 - d. use of only nonstimulants to treat ADHD in adolescents.
11. Lisdexamfetamine dimesylate is
 - a. a long-acting amphetamine delivered via a patch.
 - b. an amphetamine prodrug that is inactive until metabolized.
 - c. a form of amphetamine contained in an enteric-coated capsule.
 - d. an extended-release OROS formulation.
12. Which of the following statements is reflected in the practice parameters for ADHD treatment issued by the American Academy of Child and Adolescent Psychiatry?
 - a. Children with ADHD should be started at the highest allowable dose of a stimulant for their age and weight.
 - b. Children being treated with stimulants for ADHD should be seen weekly during the first 3 months of therapy.
 - c. When children are being treated with stimulants for ADHD, it is critical to have reliable information about behavioral changes from teachers.
 - d. Parents are not an important source of information about behavioral changes in children being treated with stimulants for ADHD.
13. The FDA Pediatric Advisory Committee in March 2006 questioned the safety of modafinil for pediatric patients due to
 - a. concerns about excessive wakefulness.
 - b. concerns about depression of appetite.
 - c. concerns about the possible development of Stevens-Johnson syndrome.
 - d. concerns about increased distractibility.
14. Overall results from the Multimodal Treatment Study of ADHD (MTA) suggest that
 - a. the best outcomes resulted from community care.
 - b. the best outcomes resulted from the use of high-dose stimulants.
 - c. the best outcomes resulted from intensive medication management, alone or combined with behavioral therapy.
 - d. The best outcomes resulted from a combination of nonstimulant therapy and behavior therapy.
15. Which of the following is true regarding cardiac evaluation before prescribing a stimulant medication for a patient with ADHD?
 - a. There is no evidence of need for routine cardiac evaluation such as electrocardiogram before stimulant treatment in otherwise healthy individuals.
 - b. Routine cardiac evaluation including electrocardiogram should be done in all new patients.
 - c. The patient should be seen by a cardiologist.
 - d. A cardiology consult should be arranged even if there is no family history of heart disease.

16. The FDA recommended labeling changes noting that aggression can be part of ADHD. What was FDA's further advice to physicians?
 - a. Aggression can be decreased with stimulant treatment.
 - b. New episodes or exacerbation of aggression should be discussed with the physician.
 - c. The physician should consider stopping the medication.
 - d. All of the above.
17. Clinical experience suggests that most children treated with stimulants
 - a. experience a 20% below-expected growth deficit.
 - b. experience a slower growth rate early in therapy that attenuates and ultimately disappears.
 - c. experience no growth deficit during treatment.
 - d. experience a surge in growth early in treatment that attenuates and ultimately disappears.
18. Studies have demonstrated that most diversion or misuse of stimulants is associated with extended-release agents.
 - a. True
 - b. False
19. Which of the following is most often true regarding treatment of adults with ADHD and a comorbid psychiatric disorder?
 - a. The comorbid disorder—particularly SUD, depression, or bipolar or anxiety disorders—should be treated only after the ADHD is under control.
 - b. A medication should be prescribed that is effective for both ADHD and the comorbid disorder; for example, a stimulant if the patient is depressed.
 - c. The comorbid disorder—particularly SUD, depression, or bipolar or anxiety disorders—should be treated first.
 - d. ADHD should be treated first if the comorbid disorder is SUD.
20. The Texas Children's Medication Algorithm Project
 - a. provides an evidence-based stepwise treatment plan for ADHD using an overall disease management approach.
 - b. is targeted for a specific subpopulation of ADHD sufferers living in a particular region of the Southwest.
 - c. describes psychoeducational alternatives to the use of medication for ADHD.
 - d. does not include strategies for treating ADHD that is accompanied by comorbid psychiatric conditions.

To complete this activity, go to www.amcp.org (Learning Center/Online CE), where you will access the posttest and evaluation form.

NOTES

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