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SPECIAL EDITION

Assessing the Safety of ADHD Medications

An Expert Panel Considers the Clinical Significance
of Potential Adverse Effects

CME-Certified Monograph

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Jointly Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ)—Center for Continuing and Outreach Education and **Medical Crossfire®**/Liberty Communications Network



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Educational Overview

Despite their extensive use over time, the safety profiles of ADHD medications, including stimulants and nonstimulants, continue to be scrutinized in media reports and in the medical literature. Greater insight is needed into the incidence, scenarios, and clinical significance with which adverse effects such as cardiac events and sudden death, hepatotoxicities, and growth suppression may occur in specific patients treated with ADHD medications. Because withholding these agents has consequences of its own, clinicians must balance the actual risk of these potential effects against the well-documented risks of not treating ADHD.

This *Medical Crossfire*® activity, conducted in conjunction with the University of Medicine & Dentistry of New Jersey, will confront these and other issues related to the management of ADHD in pediatric and adult populations.

Target Audience

This educational activity is designed for psychiatrists, pediatricians, primary-care physicians, neurologists, and other health care professionals interested in or involved with managing patients with ADHD.

Learning Objectives

Upon the completion of this activity, participants should be able to:

- Clarify the potential adverse effects associated with ADHD medications, including cardiovascular effects and sudden death, hepatotoxicity, and growth suppression.
- Consider the clinical significance of these effects, and identify strategies physicians might employ to minimize them.
- Weigh the importance and benefits of treatment versus the medical, social, and developmental implications of nontreatment.

Method of Instruction

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test consisting of a series of multiple-choice questions.

The activity is complemented with references that contain the rationale for the correct answer to each self-assessment question as well as a description identifying the section of the activity that contains the correct answer, allowing participants to review the material as needed, thus finalizing their educational participation.

Upon completing this activity as designed, participants will receive a letter of credit awarding *AMA PRA Category 1 Credit*™ three to four weeks after receipt of the registration, and evaluation materials.

Estimated time to complete this activity as designed is one (1) hour.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of UMDNJ–Center for Continuing and Outreach Education and *Medical Crossfire*/Liberty Communications Network. UMDNJ–Center for Continuing and Outreach Education is accredited by the ACCME to provide continuing medical education for physicians.

UMDNJ–Center for Continuing and Outreach Education designates this educational activity for a maximum of *1 AMA PRA Category 1 Credit*.™ Physicians should claim credit commensurate with the extent of their participation.

The print monograph was peer-reviewed for relevance, accuracy of content and balance of presentation by Javier I. Escobar, MD, and pilot-tested for time required for participation by Shanthi Lewis, MD; John F. Schiltz, MD, PhD; and Cindy Yeung, DO.

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Disclosure Declarations

In accordance with the disclosure policies of UMDNJ and to conform with ACCME and FDA guidelines, individuals in a position to control the content of this education activity are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with proprietary entities producing health care goods or services, with the exemption of non-profit or government organizations and non-health care related companies, within the past 12 months; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Faculty Disclosure Declarations

Dr. Adler has received grant/research support from Abbott Laboratories, Bristol-Myers Squibb, Eli Lilly and Co., McNeil/Johnson & Johnson, Merck & Co., Inc., Neurosearch, Novartis Pharmaceuticals Corp., Pfizer Labs, and Shire Pharmaceuticals; has been a consultant for Abbott Laboratories, Bristol-Myers Squibb, Cortex Pharmaceuticals, Eli Lilly and Co., Kyowa Pharmaceuticals, McNeil/Johnson & Johnson, Merck & Co., Inc., Neurosearch, Novartis Pharmaceuticals Corp., Pfizer Labs, and Shire Pharmaceuticals; and has served on the speakers' bureaus of Abbott Laboratories, Bristol-Myers Squibb, Eli Lilly and Co., McNeil/Johnson & Johnson, Merck & Co., Inc., Neurosearch, Novartis Pharmaceuticals Corp., Pfizer Labs, and Shire Pharmaceuticals Inc.

Dr. Biederman has received grant/research support from Abbott Laboratories, Bristol-Myers Squibb, Cephalon, Eli Lilly and Co., Janssen Pharmaceutica Products, Lilly Foundation, Neurosearch, New River Pharmaceuticals, Pfizer Labs, Prechter Foundation, Stanley Medical Institute, Ortho-McNeil Pharmaceuticals, and Shire Pharmaceuticals Inc.; has served on the speakers' bureaus of Cephalon, Eli Lilly & Co., Ortho-McNeil Pharmaceuticals, and Shire Pharmaceuticals Inc.; and is on the advisory boards of Cephalon, Janssen Pharmaceutica Products, Novartis Pharmaceuticals Corp., Ortho-McNeil Pharmaceuticals, and Shire Pharmaceuticals Inc.

Dr. Dodson has been a consultant for, and served on the speakers' bureaus of Shire Pharmaceuticals Inc. and Novartis Pharmaceuticals Corp.

Dr. Escobar, Dr. Lewis, Dr. Schiltz, and Dr. Yeung have no financial arrangements or affiliations to disclose.

Dr. Findling has received grant/research support from Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Celltech-Medeva, Forest Laboratories, GlaxoSmithKline Pharmaceuticals, Johnson & Johnson, Eli Lilly & Co., New River Pharmaceuticals, Novartis Pharmaceuticals Corp, Otsuka America Pharmaceutical, Pfizer Labs, Shire Pharmaceuticals Inc., Solvay Pharmaceuticals, and Wyeth Pharmaceuticals; has been a consultant for Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Celltech-Medeva, Forest Laboratories, GlaxoSmithKline Pharmaceuticals, Johnson & Johnson, Eli Lilly & Co., New River Pharmaceuticals, Novartis Pharmaceuticals Corp., Otsuka America Pharmaceutical, Pfizer Labs, Sanofi-Synthelabo Pharmaceuticals, Shire Pharmaceuticals Inc., and Wyeth Pharmaceuticals; and has served on the speakers' bureau of Shire Pharmaceuticals Inc.

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It should be noted that the recommendations made herein with regard to the use of therapeutic agents, varying disease states, and assessments of risk, are based upon a combination of clinical trials, current guidelines, and the clinical practice experience of the participating panelist. The drug selection and dosage information presented in this activity are believed to be accurate. However, participants are urged to consult the full prescribing information on any agent(s) presented in this activity for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects before prescribing any medication.

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Assessing the Safety of ADHD Medications

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Attention-deficit/hyperactivity disorder (ADHD)—a neurophysiologic disorder characterized in behavioral terms—is one of the most common psychiatric disorders that appears in children and often persists into adulthood.¹⁻³ Up to 80% of diagnosed hyperactive children exhibit symptoms of ADHD that persist into adolescence, and as many as 65% into adulthood.⁴ While medications to treat ADHD have been extensively studied, deemed safe and efficacious, and considered a preventative measure against problems later in life, the safety of these medications has again become a subject of discussion.^{1,2} During this **Medical Crossfire**, experts in neurology; pediatric, adolescent, and adult psychiatry; and pediatric psychopharmacology discuss the clinical significance of the adverse reactions associated with ADHD medications, the risk-benefit ratio of treatment versus nontreatment, and effective strategies for addressing questions about safety in clinical practice.

ADHD Medications: Should Clinicians Be Concerned?

To lead off this *Medical Crossfire*, moderator Peter L. Salgo, MD, asked the panel if the current ADHD medications are safe, and if clinicians should be concerned about prescribing them for their patients.

“These medications are absolutely safe,” declared Joseph Biederman, MD, who added that the agents “have extraordinary safety records. Stimulants such as amphetamine and methylphenidate compounds have been clinically used for many decades in millions of children, and more recently in adults.” In terms of approved nonstimulants, he remarked that, “atomoxetine has been extensively investigated in clinical trials and extensive multi-year follow-up studies in individuals in both pediatric and adult age groups. So the reality is that these are very safe medications appropriate for use in children as well as adults,” concluded Dr. Biederman.

Heightened concerns surrounding the safety of ADHD medications have recently been published in the news and medical literature⁵⁻⁷, and Dr. Biederman offered that this controversy surrounding ADHD medications is two-fold. He explained that some of the concern stems from individuals and groups that possess strong beliefs and prejudices against medication use in general, especially in children, “particularly high-profile medications such as those used in the treatment of ADHD.” The second aspect of this concern, Dr. Biederman continued, revolves around safety and the potential for abuse with stimulant medications.

“There is a kind of mythology that the use of stimulants, particularly in children, promotes drug-seeking behaviors.” Contrary to this myth, Dr. Biederman emphasized that stimulant medications “are protective and do not enhance drug-seeking behavior.” In fact, the National Institute of Mental Health recognizes that proactive use of ADHD med-

ications in children may actually prevent addictions and emotional problems later on in life.¹

Additionally, noted William W. Dodson, MD, in support of this assertion, “Eight consecutive studies have shown a prevention of the development of substance use disorders to begin with.”⁸

Lenard Adler, MD pointed out that “both stimulant and non-stimulant medications [mixed amphetamine salts extended release, and atomoxetine, respectively] approved for adult ADHD are generally safe and highly effective in treating adults with the disorder. These medications play primary roles in the long-term treatment of adults with ADHD.”

Focus on Cardiac Safety and Sudden Death

Recently, the cardiac safety of pharmacological therapy for ADHD became a focus of FDA scrutiny. Both the stimulant and non-stimulant medications used to treat ADHD have the effect of increasing both blood pressure and pulse rate. While these increases are statistically significant, they were not clinically significant in either children⁸ or adults.⁹ In 2006, the FDA changed the wording of the class warning for all of the stimulant class medications for patients with preexisting cardiovascular conditions.

This change of wording, however, did not rise to the level of a black box warning, explained Dr. Dodson. “It was based on the FDA’s own data from 1999 to 2004 on the sudden unexplained deaths of people under the age of 18 who were taking methylphenidate, amphetamine, or atomoxetine,” he noted. “Minor cardiac outflow abnormalities were found in four of the 20 autopsies performed. These were incidental findings and not thought to be related to the cause of death. In none of the cases was the cause of death found to be related to the fact that the person was taking medication for ADHD.” Nonetheless, the FDA added a class warning

for physicians to be vigilant for preexisting cardiovascular disease and especially for cardiac outflow abnormalities.

“In many ways these data should be reassuring,” continued Dr. Dodson, who offered pertinent statistics. The background rate of sudden cardiac death in prepubertal children is between 1.3 and 2.4 unexpected deaths per 100,000 children per year.¹⁰ Among persons taking medication for ADHD, the incidence was: methylphenidate, 0.2 per 100,000 person-years of exposure; amphetamine, 0.3 per 100,000 person-years of exposure; and atomoxetine, 0.5 per 100,000 person-years of exposure.¹¹

“The risk for all three medications was well below the risk found in the general population for the same age and gender,” pointed out Dr. Dodson. “Therefore, the new FDA warnings probably represent an abundance of caution.” In fact, he stated, the American Heart Association guidelines do not recommend any special workup or treatment monitoring (including EKG, ECHO, or treadmill testing, etc.) for persons taking ADHD medications unless there is a clinical indication for such testing.¹²

With the recent FDA warning as background, Dr. Salgo launched a discussion of cardiac safety and sudden death in the setting of pharmacological therapy for ADHD. “What are the potential cardiac events associated with ADHD medications and what do the studies evaluating cardiac effects of these medications suggest?” asked Dr. Salgo.

“Certainly there are case reports of unfortunate events associated with the use of psychostimulants, but again, these agents have a safe and effective track record and overall, a very favorable cardiovascular profile,” replied Robert L. Findling, MD. Referring to the unique instance that an occasional and severe adverse effect occurs in an individual taking an ADHD medication, Dr. Findling advised that, “these events do not necessarily mean that they were actually caused by these agents.”

In the clinical setting, obtaining a thorough medical history, blood pressure, and heart rate are important prior to the initiation of ADHD medications.¹³ In patients who present with cardiac abnormalities, conduction defects, and blood pressure problems, especially brittle hypertension, Dr. Biederman suggested that, “these medications could result in an unfavorable effect, however, in patients without cardiac disease or blood pressure concerns, these medications have minimal impact on the cardiovascular system.”

According to Dr. Biederman, there is a vast amount of data documenting the cardiovascular safety of the stimulants and nonstimulants medications that indicate, “both the stimulants and nonstimulants are extraordinarily safe, and have minimal impact on blood pressure, heart rate and the electrocardiogram.” He added that ADHD medications “tend to produce very small increases in diastolic and systolic blood pressure, and increase heart rate a few beats per minute.” In consideration of these effects, however, he affirmed that, “these changes are very minor and do not put patients in jeopardy.”

The American Heart Association issued a scientific statement in 1999 highlighting that the cardiovascular effects of methylphenidate, dextroamphetamine, and pemoline are clinically insignificant, and that in the absence of cardiovascular concerns, these medications require no additional cardiovascular monitoring (e.g., EKGs).¹⁴ Subsequent clinical trials have observed clinically insignificant but statistically significant changes in blood pressure and heart rate, not limited to the stimulants.^{7,14-16}

In response to discussion raised on the topic of sudden death and ADHD medications, Dr. Biederman remarked that, “What needs to be communicated to clinicians regarding sudden death is that it is a natural occurrence in the general population. There is a base rate of sudden death in the general population from infancy onwards, and the older an individual gets, the higher the rate gets.”¹⁷

Cardiac toxicity associated with stimulant use in ADHD has been featured in the media as the Canadian drug regulatory agency, Health Canada, recently raised concerns about mixed amphetamine salts extended release in the treatment of ADHD. This action was based on US FDA post-marketing surveillance reports of sudden death in pediatric and adult patients taking the medication. Out of the approximately 20 reported deaths, nearly 50% of patients were found to have either undiagnosed cardiac abnormalities, were complicated by other illness, exercised rigorously, or had above-toxic levels of amphetamine.^{5,6,18}

Alluding to such recent reports of sudden death in patients taking controlled-release amphetamine preparations for ADHD, the panel provided further insight on the actual occurrence of sudden death in these instances compared with the rate of sudden death in the general population. “In the approximately 20 cases of sudden death reported,”^{5,6,19} observed Dr. Biederman, “if you were to consider the total number of individuals treated in conjunction with the total number of prescriptions—approximately 4 million just for the formulation of mixed amphetamine salts extended release made by Shire (not including generics)—the resulting rate is not larger than that of what would be expected by chance alone.” In the tragic instance where an individual takes a medication and then experiences sudden death, “it is not necessarily true that there is always a causal relationship between the two,” he concluded.

Offering the practitioner perspective, Dr. Dodson suggested that, “if you fine-tune the medications, there are very few effects on the cardiovascular, or any other, system.” Commenting further on the safety of ADHD medications, he concurred with the views expressed by his colleagues. “These are really some of the safest medications ever brought to market.”²⁰ Acknowledging their long history of use, he noted, “a lot of people forget that for 50 years, amphetamine was an over-

the-counter nasal spray decongestant, and that, most of these products have been on the market for 50 to 70 years.” With the extensive use and long history of these medications, Dr. Dodson remarked that “there is nothing about these medications that is going to jump up and surprise us.”

As a result of the recent focus of the health care community on the safety of ADHD medications, the American Academy of Child and Adolescent Psychiatry released the following recommendations for clinicians considering controlled-release amphetamine products:

- Include a thorough psychiatric and medical history in the context of a comprehensive evaluation when a child presents with symptoms of ADHD or any other disorder.
- Continue to follow FDA practices set forth prior to, and since, recent reports of sudden unexplained death.
- Describe and discuss with patients and guardians the risks and benefits associated with all ADHD medications.
- Monitor the patient on a schedule tailored to the patient and their medical history.¹⁸

“Are the effects that we have been discussing limited to specific medications, or are we looking at class effects?” queried Dr. Salgo.

“These are clearly class effects,” remarked Dr. Dodson, who added that the effects are “essentially the same no matter which agent you happen to choose or which agent the patient responds the best to.”

Cardiovascular effects are not isolated to the stimulant drug class, as they have been observed in nonstimulant drugs such as selective norepinephrine inhibitors (SNRIs) used to treat ADHD. Adverse effects that have been documented include heart rate, blood pressure, and cardiac rhythm abnormalities. The SNRI atomoxetine has been associated with minimal statistically significant increases, although clinically insignificant, increases in pulse rate and blood pressure.¹⁵

Dr. Salgo continued the discussion by asking the panel how patients treated with ADHD medications should be monitored. “Is any special monitoring necessary?” he inquired.

“A good doctor will be vigilant for cardiovascular events,” replied Dr. Dodson, adding that “most physicians who prescribe these medications will take blood pressure and pulse each time the patient comes in. You are going to take the same prudent precautions as you would with any patient. This is not something new, different or threatening, but good, simple medical practice.”

Following up on Dr. Dodson’s comments, Dr. Findling directed the panel’s attention to the AHA’s scientific statement on cardiovascular monitoring of children and adolescents receiving psychotropic drugs (See **Figure 1**). He summarized that these recommendations suggest that in the absence of any warnings, “cardiovascular monitoring is likely not necessary for youngsters without any cardiovascular disease.”

In the absence of data, he continued, clinicians should “monitor children and adults with cardiovascular disease more closely.” Reflecting on his clinical experience, Dr. Findling mentioned that he adopts the more conservative approach and admitted that, “I will monitor blood pressure and pulse to ensure there is no idiosyncratic rise in blood pressure or in pulse rate. In years of practice, I have only observed these increases in two patients, and they were not by any means clinically significant.”

“Taking a thorough medical history and monitoring vital signs is just the safe and prudent practice that most physicians already carry out,” noted Dr. Dodson. In addition to executing these basic clinical practices, he discussed the importance of patient communication and reassurance. Clinicians, he observed, “must be able to convey to the patient that these medications are safe, and are supported by official organizations such as the FDA, the American Academy of Child

and Adolescent Psychiatry, and the AHA.” He concluded that these official organizations have evaluated the safety of ADHD medications and deemed that these are safe medications and that no special cardiac work-up or monitoring is required.^{13,14,18,19}

The presence of certain cardiac conditions (See **Figure 1**), remarked Dr. Biederman, should “prompt clinicians to refer the patient to an adult or pediatric cardiologist to ensure that there is nothing more worrisome in the cardiovascular system that requires further attention.” Precautions such as inquiring about cardiovascular standing, family history of sudden death, or other uncommon non-coronary events prior to initiating ADHD medications is “something that clinicians should be mindful of.”^{2,13}

Although he acknowledged that extra measures such as medical histories and assessing cardiac health are important, Dr. Findling reflected back on clinical trial data, and underscored that, “most studies of stimulants exclude patients with significant cardiovascular histories based on the presumption that they may be more sensitive to stimulant effects. However, there are no research data regarding the use of stimulants in this population. Thus, whether or not these patients with cardiovascular histories are truly vulnerable or not, remains an empiric question.”

“Dr. Findling is absolutely correct. The black-box warning that has been put on the controlled-release amphetamine preparations is based on the absence of knowledge,” confirmed Dr. Biederman. He pointed out that the black-box warning mentions that individuals with structural cardiac anomalies should not be exposed to compounds that are not fully known or investigated. Indicating that there are many individuals who have a wide range of cardiovascular conditions, Dr. Biederman contended that cardiologists “would not necessarily recommend that all cardiac patients who require ADHD medications and are eligible for treatment should

not receive pharmacological treatment solely based on the fact that they have a structural cardiac anomaly.”

Acknowledging that further investigation of the drug class is warranted, especially in patients with cardiac anomalies, Dr. Biederman asserted that in this subpopulation, ADHD medication “is not an absolute contraindication,” and sending a patient for a cardiac consult is a cautious approach in these instances.

FIGURE 1

The AHA’s scientific statement on cardiovascular monitoring of children and adolescents receiving psychotropic drugs recommends taking medical histories to identify patients with:

- Arrhythmia
- Known electrocardiographic structure obstructer
- Cardiac anomalies
- History of palpitations
- History of chest pain, and
- Histories of fainting¹²

The AHA specifically recommends that prior to the start of psychotherapeutic agents in pediatric patients:

- A careful medical history should be obtained
- Medication use is documented
- Family history, especially long-QT syndrome and instances of sudden death are noted
- Follow-up visits should reveal if the patient has added any other drugs or experienced any cardiac abnormalities
- Physical examination should include heart rate and blood pressure measurements¹²

Focus on Hepatotoxicity

Turning the discussion to the topic of hepatotoxicity, Dr. Salgo inquired, “How common is hepatotoxicity in patients treated with ADHD medications, and what do the data demonstrate?”

“There really does not seem to be any substantial hepatic risk associated with the prototypic psychostimulants, the methylphenidates, and the amphetamines,” remarked Dr. Findling. “Certainly, great concern has been raised regarding pemoline due to hepatocellular damage associated with its use,” he noted.

In addition to pemoline, the potential risk of hepatocellular toxicity associated with the use of the nonstimulant atomoxetine has been noted. “A bolded warning was added to the package insert for atomoxetine suggesting that this medication should be discontinued in patients who develop signs of jaundice or other hepatic illness,” Dr. Findling explained, noting that hepatotoxicity associated with the use of atomoxetine “is really the result of at least two cases of liver damage that occurred in the context of millions of individuals receiving this agent.”²¹

In December 2004, the FDA issued a warning and changed the package labeling for atomoxetine in response to two cases of severe liver toxicity in one adult and one teenager who were taking atomoxetine. Both patients completely recovered after discontinuation of the medication.

“This is, indeed, a very rare occurrence, given the fact that more than 2 million people have taken atomoxetine since it was introduced in 2002,” agreed Dr. Dodson. “There were no cases of hepatotoxicity in the pre-marketing clinical trials, which involved more than 6,000 different individuals.” He cautioned clinicians to be vigilant for the signs and symptoms of liver injury, including jaundice, dark urine, upper-right-quadrant abdominal tenderness, and unexplained flu-like symptoms. “The medications should be immediately discontinued in patients who

develop either the physical signs or laboratory evidence of liver toxicity,” advised Dr. Dodson.

“What then is the clinical significance of hepatotoxicity in patients treated for ADHD?” inquired Dr. Salgo.

“In general, hepatotoxicity is an occurrence that has not yet been fully explained,” stated Dr. Dodson, suggesting that hepatotoxicity should be evaluated on a case-by-case basis. For example, he noted, “We treat patients as individuals, and if a patient came along with a long history of alcoholism, hepatitis C, or something that was compromising the liver, a clinician might be hesitant to use an agent that has shown problems with liver functioning.”

Dr. Biederman contended that “neither the stimulants nor atomoxetine are hepatotoxic. Side effects of certain drugs occur in a rare, idiosyncratic fashion.²¹⁻²³ Therefore, performing liver function tests is essentially useless in my view.”

Lenard Adler, MD, agreed with his colleague, and further stressed that, “these reported cases were idiosyncratic in nature, and there was no hepatotoxicity observed in any of the clinical trials.”

Dr. Biederman noted that he “would not put atomoxetine in the same group as valproic acid or pemoline, which can cause severe hepatotoxic effects.” Pemoline, for example, has been associated with life-threatening liver toxicity.^{24,25} When treating patients with liver disease, he recommended that clinicians be cautious with all medications that are metabolized primarily by the liver. “It is the obligation of clinicians to distinguish absolute risk from relative risk when

“It is the obligation of clinicians to distinguish absolute risk from relative risk when it comes to treating patients.”

—Dr. Biederman

it comes to treating patients who have liver dysfunction with ADHD medications,” stated Dr. Biederman. He recommended that patients should immediately contact their physicians if they experience jaundice or changes in stool or urine color, as this may indicate a cause for concern.

Dr. Findling underscored that “it is important to understand that unfortunate events do occur.” What needs to be resonated and retained, he suggested, is that “association is not the same thing as causation,” and he advocated a cautious, thoughtful approach when evaluating the significance of hepatotoxicity in patients treated with ADHD medications. Furthermore, he emphasized that, “it is also important to not respond to ideas or inferences in the absence of empiric data and suggest that a conclusion must be formulated.” Until proven otherwise, and in the absence of solid data coupled with the millions of patients treated with these medications, Dr. Findling concluded that “it is premature to declare that hepatotoxicity is related to treatment.”

Offering a final thought on this issue, Dr. Adler stressed that, “these reported cases were idiosyncratic in nature and there was no hepatotoxicity in any of the clinical trials.”

Focus on Suicide

It is widely understood that response to antidepressant medication is different in children and adolescents than it is in adults. Although atomoxetine did not separate from placebo in its initial clinical trials as an antidepressant, the FDA still included atomoxetine in its general class warnings concerning a 2% increase in suicidal thoughts found in a meta-analysis of a large number of short-term studies of antidepressant medication in the pediatric population. In a review of the 12 pediatric studies involving atomoxetine, the risk of suicidal ideation was 5 of 1,357 (or 0.4%) for persons taking atomoxetine versus 0 of 851 for persons taking placebo.²⁶ There

was one suicide attempt. There was no evidence of an increased risk of suicidal thinking in adults taking the medication.

“The true meaning of these data is unclear,” stated Dr. Dodson, given the fact that there is a great deal of evidence that persons with ADHD are at higher risk for self injury and suicide.²⁷ “Therefore, for the time being,” recommended Dr. Dodson, “clinicians should take a good clinical history, listening for evidence of a comorbid condition such as depression or bipolar mood disorder. Both adolescent patients and their parents should be warned about the small risk of increased suicidal ideation and should be asked to notify the clinician if this develops.”

Focus on Growth

“What are the findings about the effect of ADHD medications on growth, and are these results significant?” Dr. Salgo inquired.

“Height is a genetic trait,” began Dr. Biederman. Citing his findings from a study of boys taking ADHD medications, he and his colleagues observed that, “unrelated to the medication, there appears to be a deceleration of growth, or rather the tempo of growth is slowed down in boys with ADHD by mid-adolescence. But,” he declared, “there is no evidence that final height, or the height that is expected to be attained at the end of adolescence relative to the genetic endowment of height correlated to parental height, is affected by the medications.” Dr. Biederman pointed out that growth deceleration that occurs in mid-adolescent boys is not related to ADHD medications, and that this phenomenon has not been observed in girls.^{28,29}

To illustrate his point, Dr. Biederman offered the following example: “A mid-adolescent boy, age 13 or 14, is taking ADHD medications and is growing at a tempo that may be comparatively slower than his peers. A clinician may deduce that the medication is the causative factor. But because two things happen at the same time, that does not nec-

essarily mean that one caused the other.” Based on his clinical expertise, Dr. Biederman considers the evidence from clinical trials “reassuring, particularly results obtained from long-term follow-up studies of the stimulants, which documented a very small effect on growth and height in children.”^{28,30}

The National Institutes of Mental Health is sponsoring an ongoing, multisite, cooperative agreement treatment study of children with ADHD, known as The Multimodal Treatment Study of Children With Attention Deficit Hyperactivity Disorder, or MTA.¹ One of the issues examined in the MTA is growth suppression during 14- and 24-month follow-ups in subgroups receiving the above-mentioned treatments. The MTA group observed significant growth suppression effect during the second year of treatment in subgroups that were continuously treated with medication relative to unmedicated children. However, children in the unmedicated group were taller than normal children and grew at a faster rate than those who were medicated and who maintained their standardized height. Based on these problematic calculations, the MTA reported that growth suppression effects (1 cm/year and 1.25 kg/year) during the follow-up phase could be related to medication effect, with the continuously medicated subgroup experiencing slower growth compared with the unmedicated subgroup.

Commenting on the MTA data, Dr. Biederman pointed out that “The analytic approach taken by my colleagues in the MTA may have been problematic as they compared growth in children that were receiving behavioral treatment who were very large to begin with.” He further clarified that, “these children continued to grow at unmatched speeds relative to the medicated group. These comparisons were made with a group of children that, for peculiar reasons, experienced an accelerated rate of growth and compared these individuals with children who did not grow as much. Therefore, growth amounts

between two extremes appear to have produced the reported results.”

He further elaborated that, “most of the studies that assessed height in children with ADHD were of sufficient duration to examine ‘final height’ or rather the height that an individual would achieve at the end of their development,” as most of the subjects in these studies involved children younger than 12. Two- and three-year follow-ups were conducted, which according to Dr. Biederman, would evaluate these children in mid-adolescence.³¹

Regarding these disparities in growth among the MTA treatment groups, Dr. Biederman outlined that the “standardized growth values in the children in the MTA who were medicated and followed-up for two years do not support the hypothesis that the stimulants interfered with growth or height in those children.” When the growth-suppression statistics compare those children who grew at an accelerated speed and did not take medication, this “creates an artificial impression that stimulants delayed growth and height.” Dr. Biederman added that, “I do not believe behavioral treatment promotes growth and height.”³¹

“Even in the worst case scenario, the degree to which stature appears to be affected by psychostimulants, even in the most grim reports, is extremely modest,” offered Dr. Findling. He speculated that when reports of growth issues associated with these medications are communicated, “there is a concern that patients treated with these compounds will end up extraordinarily short, and that is certainly not what any of the data are indicating.” Ultimately, Dr. Findling stated, “it is important to recognize that if a growth effect is experienced, it is small and certainly not clinically significant.”³⁰

Following up on Dr. Findling’s comments, Dr. Biederman articulated that “When clinicians treat patients, they deal with individuals, and when clinicians deal with data, they are dealing with the aggregate.” According to Dr. Biederman, “there

“It is important to recognize that if a growth effect is experienced, it is small and certainly not clinically significant.”
—Dr. Findling

are two important aspects to growth in children taking ADHD medications that must be considered. First, some individuals may grow at different rates, which may not always be the desired growth rate and, second, growth is dependent on parental height.”

If growth is a patient, physician, or parental concern, Dr. Biederman suggested that “one approach is to perform a radiologic analysis of bone age to estimate if the child is behind in growth in height.” Consulting a pediatric endocrinologist, he suggested, is another strategy which may relieve parental anxiety surrounding the growth of their child and help validate clinician reassurance.

Weighing the Risks and Benefits of Treatment vs. Nontreatment

“What have studies demonstrated with respect to the consequences of untreated ADHD?” queried Dr. Salgo.

“There are significant impairments that occur in individuals, certainly in adults with ADHD, if they remain untreated,” remarked Dr. Adler. Emphasizing the magnitude of undertreatment, he reported that recent surveys demonstrated that, “probably only 1 in 5 adults with ADHD are aware they have this condition and seek treatment.”³² He stated that data demonstrate “substantial impairments” in adults, and a “greater risk of smoking cigarettes and abusing substances” in adolescents. An important point to convey, he noted, “is that the risk of substance abuse appears to be much greater if ADHD is untreated.”^{33,34}

Evidence from long-term studies further demonstrates that comorbidity associated with childhood and adolescent ADHD persists until adulthood.³⁵ Results from longitudinal studies of subtypes of ADHD related to substance use disorders demonstrated that ADHD is a risk factor for smoking and substance abuse. The age of onset of substance abuse in comorbid children and young adults

with ADHD was 12 to 16 years and 17 to 22 years in noncomorbid cases. Moreover, the age of onset was earlier in females with ADHD compared with males.³⁶

In children, Dr. Findling remarked that ADHD affects a number of parameters such as school performance and social interaction with family members, loved ones, and even peers. He added that “all of these interactions are vitally important to a child, and if left untreated, these personal and profound impairments remain with the child and they truly suffer as a result of their difficulties.³ Why would you want to let a child suffer unnecessarily?” posed Dr. Findling rhetorically.

“The evidence that ADHD is an extraordinarily morbid condition is overwhelming,” declared Dr. Biederman. Based on extensive 10-year follow-up studies, “There is not a single variable from educational attainment, satisfaction with life, substance abuse, cigarette smoking and relationship problems; from multiple variables that were used in any domain or function imaginable that boys and girls with ADHD are not substantially worse on average,” he reported. “These are group data and not every child with ADHD has a negative prognosis. However, in general, ADHD is an enormously morbid, costly, and potentially devastating condition.”³⁵

Beyond morbidity, the financial aspect of ADHD is profound. Dr. Biederman reported that the average individual with ADHD, who has a similar educational background to an individual without the condition, “makes \$10,000 less per year in income.” When the prevalence of ADHD, “which is approximately 4%,” is combined with the cost of underemployment in individuals with ADHD, “this totals approximately \$100 billion each year,” he explained.

Dr. Biederman pointed out that the financial impact of ADHD is even greater when “the costs of substance abuse, depression, and other psychiatric comorbidities, and learning disabilities are considered. One can argue that ADHD is among the costliest

conditions,” he reasoned. “ADHD can profoundly impact every life aspect of a child, adolescent, and adult. Untreated ADHD translates into enormous costs and unnecessary suffering.”^{34,37,38}

According to Dr. Dodson, clinicians need to communicate to their patients, families, and caregivers that ADHD impairments manifest in many facets of life. “ADHD can rear its ugly head everywhere,” he noted, pointing out that “the common misperception is that ADHD is just an academic problem. ADHD impairments transcend academics and may involve an increased risk of motor vehicle accidents and substance abuse, issues related to sexuality, and involvement with the law.” ADHD treatments have been “demonstrated to be effective and preventative against these impairments,” and he stressed that the person affected with ADHD “needs to be taking their medication not just during school and work.” In support of this statement, he cited the fact that within their first 2 to 5 years of driving, adolescents with ADHD are in four times as many automobile accidents, are more likely to cause bodily injury in accidents, and have three times as many citations for speeding as adolescents without ADHD.¹

“Untreated ADHD carries a very ominous prognosis,” replied Dr. Biederman, and in accordance with Dr. Dodson, he acknowledged the condition’s effect on “every aspect of the individuals’ life at any age.” Although with ADHD treatments, “there are remote possibilities of issues such as cardiovascular effects, hepatotoxicity and growth impediments,” he asserted that on the whole, these events are infrequent. “The risk-benefit analysis clearly favors treatment over the risk of nontreatment,” maintained Dr. Biederman.¹

Combining Efforts: Multimodal and Pharmacological Interventions

“Where does multimodal therapy fit into the ADHD treatment paradigm?” queried Dr. Salgo.

Dr. Biederman commented that multimodal therapy, which incorporates a combination of medications plus psychosocial and psycho-educational interventions, may be useful in patients who do not achieve adequate benefit from medications,^{1,4} and “have specific learning disabilities or specific interpersonal or family issues. Particularly beneficial are cognitive behavioral interventions, which have been demonstrated to offer additional benefits than just medication alone.”

“There is certainly a role for multimodal therapy in certain patients,” asserted Dr. Adler, noting that “data coming out of Massachusetts General demonstrated that the practice of using cognitive behavioral therapies for adult patients who have had partial response to pharmacologic treatment has additional benefit.” Results from an MTA-driven trial evaluating 540 children with ADHD aged 7 to 9 years demonstrated significant superiority of behavior modification therapy versus community comparison, however, significant additional benefits of combined behavior modification therapy and medical management versus either intervention alone was not observed.³¹

Although he acknowledged the benefits of multimodal therapy, Dr. Adler pointed out that “it is important to remember that the effect of medications is robust, and that medications are a primary treatment modality in patients with ADHD throughout the spectrum of their lives.”

“How do clinicians go about maximizing treatment responses?” Dr. Salgo wondered.

“It is important to remember that, especially for adults, there is a great tendency to underdose ADHD medications,” replied Dr. Adler. “It is unlikely you will get an adequate response by prescribing for an adult a dose of methylphenidate or amphetamine product similar to a child’s dose,” he clarified. Underdosing in adults, according to Dr. Adler, may be partly responsible for the idea that “stimulants may not work as well in adults, which has not been shown in clinical trials.” Maximizing the treatment response,

Dr. Adler remarked, entails a clinical titration, and “for both stimulants and nonstimulants, this involves initiating a dose of medication and monitoring response and side effects, and a then gradual titration up to a therapeutic dose.” An appropriate dose of stimulants should have a consistent onset and duration of action in an individual patient. If a patient’s medication level drops below therapeutic level later in the day, and continues to decline, rebounding can occur, which may increase emotional lability or impulsivity, or a worsening of presenting symptoms.²

Dr. Dodson offered that, “Many of our patients are going to think in terms of high dose versus low dose, when in reality, the discussion should be changed to an explanation of what the right dose is.” Three important questions that clinicians should ask themselves when selecting ADHD medications, as identified by Dr. Dodson, include:

- 1) Is this the right molecule?
- 2) Is this the right dose?”
- 3) Is this the right timing of the dose?

By adopting these three parameters into clinical practice, he contended, “these medications are actually remarkably free of side effects, especially compared with other drugs used in psychiatry and neurology.”

Adult ADHD is a relatively new entity, noted Dr. Dodson, and “adult clinicians in medicine and psychiatry are not as accustomed to using controlled substances as the pediatricians and child psychiatrists who have used these formulations for many years in children with ADHD.” Fear, discomfort, and unfamiliarity with prescribing ADHD compounds may actually lead to underdosing in adults, he suggested.

Is Continuous Therapy Necessary?

Dr. Salgo introduced the controversial topic of drug holidays by inquiring, “Is it imperative that patients receive continuous therapy for ADHD?”

The idea of drug holidays stemmed from concerns about height with old data, according to Dr. Findling, and that “drug holidays might reverse effects associated with reduced growth rates.” Since growth impediments appear to be nominal, he advised, “these effects should certainly not be the reason to consider a drug holiday.” He added that “all things being equal, you treat children and adults in a way that is beneficial to them. If an individual is benefiting from ongoing treatment, and is tolerating treatment in the absence of any other circumstances, then they should continue with the therapy that is helping them.”

Dr. Biederman offered that, “Historically, the rationale for drug holidays in pediatrics stemmed from the banalization of ADHD as a real problem affecting life.” This theory originated with the belief that “this condition only requires intervention for school purposes, therefore, the medication was literally given during school hours and was never administered on holidays or weekends,” he clarified.

“Are there any studies that support drug holidays?” queried Dr. Salgo

“The practice of drug holidays, or planned nonadherence to medication, is regarded more a position than actual support,” answered Dr. Biederman.^{30,39}

Practical Strategies for Responding to Patient Questions about Safety

In an effort to provide practical tools to clinicians, Dr. Salgo posed the following hypothetical scenario to the panel. “Suppose that you mention to a patient or parent that you would like to initiate ADHD medication, and either of these individuals communicates concern with regard to the safety of the prescribed therapy. What are the practical strategies that clinicians can provide to their peers to effectively deal with this apprehension?”

Focusing his response on children, Dr. Findling remarked that “Ultimately, the risks that need to be considered first are those that

are associated with the condition itself.” These risks, he added, “should be put in the context of the associated risks of treatment.” Although all ADHD medications possess imperfections, they are generally safe and effective. Dr. Findling stated that clinicians should explain to the parents of children with ADHD that “in the context of the condition itself, the benefits of treatment clearly outweigh the risks of letting the child go untreated.”

With older children and adolescents, Dr. Biederman shared that the challenge lies in the fact that “patients with ADHD are often not aware that they have a problem, or at least they are not particularly insightful that ADHD is an issue.” He admitted that convincing these patients of the need for therapy can be frustrating. Despite the fact that most patients “are interested in having an intervention rather than a lecture from their physician,” he advocates that clinicians provide consultation, explanations, and provide recommendations to patients and parents about the condition and available treatments. This is especially true, as Dr. Biederman explained, in the instances of “recommending a therapeutic trial to ascertain if the medication provides relief and is well tolerated.” In order to engage patients and parents to initiate a trial of therapy, Dr. Biederman added that simply describing to patients that “we are not making a life commitment to medication but we are simply trying to gauge your response and outcome” is often helpful.

Commenting on the young adult or college-age patient, Dr. Adler focused on the importance of convincing these patients of their need for continuous therapy throughout the day. “Young adults and college-age students usually come in with the concept that they want to take their medication solely in class and not at other times of the day,” he expressed. Dr. Adler stresses the importance of concentration on tasks such as driving and studying, which illustrates that “the patient does not really know when they will need to

pay attention as life demands are often unexpected.” He concluded that, “unless we attempt to treat the adult or college-age patient throughout the day, the chance for success is vastly diminished.”¹

In the adult patient, Dr. Dodson noted that he frequently encounters resistance to treatment with ADHD medications. The underlying issue with the resistant patient, he has found, is essentially a coping mechanism. “Virtually all of these patients have somebody in their life that is going to attack them for starting medication.” According to Dr. Dodson, some patients fear that they will be criticized by the people in their lives because of their diagnosis or prescribed treatments. He believes that these patients “are really asking the clinician for defense strategies in easy-to-understand words” to use on their critics. “At least 90% of the time,” Dr. Dodson reports, “the patient can identify a person who will attack them for deciding the best approach for themselves or their child.” He concluded that “most of the battle is won” once the patient's question is revealed and he is provided with tools for responding to these situations.

Final Thoughts

In offering his takeaway message from this *Medical Crossfire*, Dr. Findling stressed that consensus exists with regard to the management of ADHD in children, adolescents, and adults. “There is empiric evidence to suggest how best to diagnose and treat the condition, and help patients. However, each patient is a unique individual and requires treatment approaches that are individually tailored to him or her,” he explained. Dr. Findling rests

firmly on the concept that “ADHD is a readily diagnosable and treatable condition for which we have very effective interventions, and a lot of good can come from accurate identification and early intervention.”

Dr. Dodson motivates patients to empower themselves with their diagnosis and treatments. “I urge individuals to make the decisions about their lives and their medical care based on knowledge rather than fears,” Dr. Dodson stated. He stressed that, “There is absolutely no harm to a trial of medication where patients can see for themselves whether or not these medications are helpful, whether or not their side effects are tolerable, and whether or not they are safe.” Based on these assessments, Dr. Dodson concluded, that “a decision based on facts and not fear should be made.”

“ADHD is a gratifying condition to treat in your practice,” summarized Dr. Adler. Reflecting on the prevalence of ADHD he highlighted that, “Certainly 10% to 20% of your patients with mood, anxiety, or substance disorders have ADHD. But we do have medications that are generally safe and highly effective that we can use to help these patients get better.”

In closing this *Medical Crossfire*, Dr. Biederman underscored “the critical importance of ADHD as a brain disorder of genetic underpinnings and a very morbid chronic illness that has a tremendous detrimental impact on all aspects of life.”¹ In light of these aspects, he declared, “the issue of treatment comes to be an important consideration relative to not treating. Therefore, the potential for improving life of our patients at any age with the extraordinary treatments we have available today is not an opportunity to pass up.” ■

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Assessing the Safety of ADHD Medications

An Expert Panel Considers the Clinical Significance of Potential Adverse Effects

CME Test

1. Prior to initiation of ADHD medications in the clinical setting, clinicians should
 - a. perform cardiovascular testing.
 - b. take the patient's medical history and perform cardiovascular testing.
 - c. obtain a thorough medical history, blood pressure, and heart rate.
 - d. perform cardiovascular testing after four weeks of pharmacological therapy.
2. Prior to initialization of psychotherapeutic agents in pediatric patients with ADHD, the American Heart Association (AHA) recommends which of the following?
 - a. medical history, and blood pressure and heart rate measurements
 - b. blood pressure measurements and liver function tests
 - c. ECG and a thorough medical history
 - d. radiologic analysis of bone age density along with heart rate and blood pressure measurements
3. The American Academy of Child and Adolescent Psychiatry recommends which of the following when contemplating controlled-release amphetamine products in children?
 - a. discuss with patients and guardians the risks and benefits associated with all types of ADHD medications
 - b. conduct thorough cardiovascular tests in all patients prior to commencing therapy
 - c. consider other stimulant or nonstimulant agents that have no cardiovascular-associated risks
 - d. conduct regular cardiovascular tests to monitor all patients while on therapy
4. Potential effects on the cardiovascular system are limited to which of the following agents?
 - a. methylphenidate, mixed amphetamine salts, and atomoxetine
 - b. methylphenidate and atomoxetine
 - c. methylphenidate and mixed amphetamine salts
 - d. mixed amphetamine salts and atomoxetine
5. In which patient should a clinician monitor ALT values?
 - a. a patient taking atomoxetine
 - b. a patient taking pemoline
 - c. a patient taking methylphenidate
 - d. a patient taking amphetamines
6. Which of the following is true regarding the impact of ADHD medications on final height?
 - a. Height is a genetic trait and is not impacted by ADHD medications.
 - b. Adolescent girls can experience a deceleration in growth due to ADHD medications.
 - c. Data indicate that ADHD medications affect the growth of adolescent boys and girls.
 - d. Drug holidays can be used to reduce the growth effects of ADHD medications.
7. Which of the following statements may explain height disparities observed in the MTA study?
 - a. Children receiving medication were not followed for a sufficient length of time.
 - b. Children who did not receive medication experienced an accelerated rate of growth.
 - c. Children who received medications had parents of short stature.
 - d. Stimulants affected the growth of children receiving this therapy.
8. If left untreated, ADHD may result in
 - a. accidents, mood disorders, income disparities, and substance abuse.
 - b. mood disorders and substance abuse.
 - c. income disparities and mood disorders.
 - d. substance abuse, accidents, and mood disorders.
9. A 2006 FDA class warning cautioned vigilance in prescribing stimulant medications for patients with
 - a. pediatric ADHD.
 - b. adult ADHD.
 - c. preexisting cardiovascular conditions.
 - d. preexisting hepatic conditions.
10. Which of the following represents current thinking on the need for continuous therapy in patients with ADHD?
 - a. The practice of drug holidays is supported by clinical trials.
 - b. Because ADHD is an academic problem, children and adolescents only need to take their medications to cover the time they are in school.
 - c. Adults do not need to take medications when not engaged in work-related activities.
 - d. Patients with ADHD should be treated the same way one would treat a patient with any other chronic illness, and thus receive continuous therapy.

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Assessing the Safety of ADHD Medications

An Expert Panel Considers the Clinical Significance of Potential Adverse Effects

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Assessing the Safety of ADHD Medications

An Expert Panel Considers the Clinical Significance of Potential Adverse Effects

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Strongly Agree Strongly Disagree

Having completed this activity, are you better able to:

Clarify the potential adverse effects associated with ADHD medications, including cardiovascular effects and sudden death, hepatotoxicity, and growth suppression. 5 4 3 2 1

Consider the clinical significance of these effects, and identify strategies physicians might employ to minimize them. 5 4 3 2 1

Weigh the importance and benefits of treatment versus the medical, social, and developmental implications of nontreatment. 5 4 3 2 1

Overall Evaluation

Strongly Agree Strongly Disagree

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Based on information presented in the program, I will (check one):

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- Do nothing. Barriers at my institution prevent me from changing my practice.

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

Please provide any additional comments pertaining to this activity (positives and negatives) and suggestions for improvement.

Please list any topics that you would like to be addressed in future educational activities.
