

## ADHD Drugs and Cardiovascular Risk

**TO THE EDITOR:** Nissen (April 6 issue)<sup>1</sup> recommends attaching a “black box” warning regarding serious cardiovascular risks to the labeling of stimulant medications used to treat attention deficit–hyperactivity disorder (ADHD). We agree that patient safety is paramount and that the long-term benefits and risks of stimulant treatment are not known definitively, yet we are concerned that such a warning will discourage patients and their families from using effective treatment. Untreated ADHD is associated with an elevated risk of substance abuse, academic failure, and motor vehicle accidents and an increased rate of psychiatric disorders.<sup>2</sup>

The 14-month, controlled Multimodal Treatment Study of Children with Attention Deficit–Hyperactivity Disorder (MTA study), sponsored by the National Institute of Mental Health, revealed a high rate of response to stimulants (more than 70 percent) and large effect sizes (0.6 to 1.2 standard deviations), with significantly lower rates of improvement for subjects who underwent psychotherapy.<sup>3–5</sup> Nissen’s concern about the use of stimulants in older adults at high risk for cardiac disease is warranted, but the article does not provide the firm evidence the Food and Drug Administration (FDA) requires to issue a black-box warning for all age groups.

Thomas Anders, M.D.

American Academy of Child and Adolescent Psychiatry  
Washington, DC 20016

Steven Sharfstein, M.D.

American Psychiatric Association  
Arlington, VA 22209

1. Nissen SE. ADHD drugs and cardiovascular risk. *N Engl J Med* 2006;354:1445-8.
2. Harpin VA. The effect of ADHD on the life of an individual, their family, and community from preschool to adult life. *Arch Dis Child* 2005;90:Suppl 1:i2-i7.
3. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder: Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry* 1999;56:1073-86.
4. Greenhill LL, Kollins S, Abikoff H, et al. Efficacy of immediate-release methylphenidate treatment for preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry* (in press).
5. Wigal T, Greenhill LL, Chuang S, et al. Tolerability and safety of methylphenidate in preschooler children with ADHD. *J Am Acad Child Adolesc Psychiatry* (in press).

**TO THE EDITOR:** We participated in the Drug Safety and Risk Management Advisory Committee, which was convened on February 9, 2006, to produce recommendations to the FDA about how best to study the rare occurrences of cardiovascular adverse events associated with medications used in the treatment of ADHD, including methylphenidate, amphetamine products, and atomoxetine.<sup>1</sup> We are concerned that a vote for a black-box warning was called without a discussion of content or language for such a warning; that the discussion did not thoroughly explore the risk associated with these medications for adults and children but implied that the risk might be higher for adults than for children; that recommendations about how best to convey the risk to children, adults, and families were not addressed; and that the concern about the increased use of these medications was confused with concern about the actual risk.

We also participated in the Pediatric Advisory Committee, which was convened on March 22, 2006, to discuss how families and physicians might best be informed of the risk associated with these medications. The discussion, which lasted for 11 hours, was informed by presentations by 7 FDA epidemiologists and physicians, 41 speakers in the public forum, and 2 representatives of pharmaceutical companies.

The Pediatric Advisory Committee recommended that the FDA include warnings, in the “highlights” section of the newly formatted labeling, that children with structural heart defects, cardiomyopathy, or heart-rhythm disturbances may be at risk for adverse cardiac events, including sudden death; that children with symptoms of psychosis and mania are at risk for adverse neuropsychiatric events; and that children require follow-up visits and the monitoring of blood pressure, pulse, and growth measures<sup>2,3</sup> (Table 1). None of the committee members, when asked directly by FDA officials, said that a black-box warning was warranted.

The committee further recommended that the FDA — with input from professional, private, and public groups — design a guide for parents and physicians that would explain the risks of these

medications in readily accessible language, modeled on successful guides used to inform parents about vaccinations for children.

We are impressed that the process of the March 22 meeting of the Pediatric Advisory Committee allowed for the airing of highly disparate and often passionate views regarding these issues. This process facilitated a frank and productive discussion by patients, family members, pediatricians, cardiologists, pharmacologists, child psychiatrists, and epidemiologists in a transparent, respectful, and public forum.

Marsha D. Rappley, M.D.

Michigan State University  
East Lansing, MI 48824  
rappley@msu.edu

John W. Moore, M.D.

UCLA Medical Center  
Los Angeles, CA 90095

Deborah Dokken, M.P.A.

2802 Blaine Dr.  
Chevy Chase, MD 20815

1. Cardiovascular risk with drug treatments for ADHD. 2006. (Accessed May 3, 2006, at <http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4210s-index.htm>.)

2. Psychiatric adverse events in attention deficit hyperactivity disorder (ADHD) clinical trials. 2006. (Accessed May 3, 2006, at <http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4210s-index.htm>.)

3. On the efficacy of pharmacological treatment of attention deficit hyperactivity disorder. 2006. (Accessed May 3, 2006, at <http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4210s-index.htm>.)

**TO THE EDITOR:** The vast increase in the diagnosis of ADHD and the frequency of treatment for the condition in children is, unfortunately, no longer a phenomenon specific to the United States. According to the latest Drug Prescription Report,<sup>1</sup> the number of daily doses of methylphenidate that are prescribed in Germany has reached 26 million per year. Although the population-adjusted volume in the United States is still 8 to 10 times that amount, the number of prescriptions for the drug for German children rose by a factor of 20 during the past 10 years, with no signs of abating. The use of methylphenidate by adults is similarly on the rise. It is to be hoped that the FDA's warning about the cardiovascular risks of ADHD drugs will curtail this worrisome development.

Leszek Wojnowski, M.D.

Johannes Gutenberg University  
D-55101 Mainz, Germany  
wojnowski@uni-mainz.de

**Table 1. Assessment of the Risks and Benefits of Medications for the Treatment of ADHD.\***

Variable	Risk or Benefit
Sudden death associated with methylphenidate, amphetamine products, and atomoxetine †	0.2 to 0.5 per 100,000 patient-years
Sudden death expected in those <18 yr of age †	1.3 to 8.5 per 100,000 patient-years
Treatment-effect size for methylphenidate and amphetamine products ‡	1.4 to 1.6
Treatment-effect size for atomoxetine ‡	0.71

\* The prevalence of ADHD in persons under the age of 18 years is approximately 5 percent.<sup>3</sup>

† Data are from the FDA.<sup>1</sup>

‡ Data are from the FDA.<sup>3</sup>

1. Schwabe U, Paffrath D. Arzneiverordnungsreport 2005. Berlin: Springer-Verlag, 2005.

**DR. NISSEN REPLIES:** Anders and Sharfstein are concerned that warnings regarding serious cardiovascular risks associated with ADHD drugs would “discourage” patients from receiving treatment. I strongly disagree. I cannot accept the paternalistic notion that patients and caregivers are better off without information about drug risks. The presence of a black-box warning and a mandatory patient guide would probably stimulate useful discussions among patients, parents, and physicians about risks, benefits, and alternative therapies. An appropriate warning might also slow the exponential growth in the use of amphetamines and similar stimulants, which has reached epidemic proportions in the United States, resulting in the treatment of nearly 10 percent of preadolescent boys.<sup>1</sup>

Rappley et al. express concern that a black-box warning was recommended by the Drug Safety and Risk Management Advisory Committee without adequate discussion of its content. Unfortunately, discussion was limited because the FDA-supplied background materials and questions for the committee did not allow for the possibility of enhanced warnings.<sup>2</sup> The committee chose an independent course of action after reviewing data regarding adverse events, including cases of sudden death, and concluded that a warning was needed. These cases included that of a 13-year-old boy who died within one hour after receiving the first dose of mixed amphetamine salts; the boy was found to have had hypertrophic cardiomyopathy on autopsy.<sup>2</sup> Advisory committees never

specify the language of such warnings, which is the responsibility of the FDA. I believe that the appearance of information in the “highlights” section of the drug label will have virtually no effect on prescribing practices. Even a boxed warning has been shown to have a minimal effect on the inappropriate use of drugs.<sup>3</sup> The table included with this letter is highly misleading. Many studies have demonstrated that only 1 to 10 percent of serious adverse events are reported to the FDA through the Adverse Event Reporting System. Accordingly, any calculation of an incidence rate for adverse events from such data is considered unreliable by FDA drug-safety staff, even for pediatric patients.<sup>4</sup>

Both letters seem to ignore a fundamental fact that increasing heart rate and blood pressure<sup>5</sup> by the administration of powerful cardiac stimulants is inherently risky. Closely related sympathomimetic amines, such as ephedra and phenylpropanolamine, have been deemed sufficiently risky that the FDA has recommended banning these agents to protect the public health.

Wojnowski expresses concern about the increase in the use of stimulants by a factor of 20 in Germany but points out that such use in the

United States is still 8 to 10 times as high. I share his concern.

The figure that appeared in my Perspective article shows an incorrect structure for epinephrine, which lacks the nonmethylated amine that is pictured. In addition, pseudoephedrine is an epimer of ephedrine, not an enantiomer, as described on page 1447.

Steven E. Nissen, M.D.

Cleveland Clinic  
Cleveland, OH 44195

1. Mosholder AD. Overview of ADHD and its pharmacotherapy. 2006. (Accessed May 3, 2006, at [http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4202S1\\_01\\_FDA-mosholder\\_files/frame.htm](http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4202S1_01_FDA-mosholder_files/frame.htm).)

2. Food and Drug Administration. Drug Safety and Risk Management Advisory Committee (DsaRM). Vol. 1. (Accessed May 3, 2006, at <http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4202t1.pdf>.)

3. Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: impact of Food and Drug Administration regulatory action. *JAMA* 2000;284:3036-9.

4. Mosholder AD, Pamer CA. Postmarketing surveillance of suicidal adverse events with pediatric use of antidepressants. *J Child Adolesc Psychopharmacol* 2006;16:33-6.

5. Wilens TE, Hammerness PG, Biederman J, et al. Blood pressure changes associated with medication treatment of adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2005;66:253-9.

Correspondence Copyright © 2006 Massachusetts Medical Society.

#### INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within three weeks after publication of the article. Letters not related to a *Journal* article must not exceed 400 words. All letters must be submitted over the Internet at <http://authors.nejm.org>. •A letter can have no more than five references and one figure or table. •A letter can be signed by no more than three authors. •Financial associations or other possible conflicts of interest must be disclosed. (Such disclosures will be published with the letters. For authors of *Journal* articles who are responding to letters, this information appears in the original articles.) •Include your full mailing address, telephone number, fax number, and e-mail address with your letter.

Our Web site: <http://authors.nejm.org>

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. Letters that do not adhere to these instructions will not be considered. Rejected letters and figures will not be returned. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal*'s various print and electronic publications and in collections, revisions, and any other form or medium.