

ADHD Drugs and Cardiovascular Risk

Steven E. Nissen, M.D.

On February 9, 2006, the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration (FDA) voted by a narrow margin — eight to seven — to recommend a “black-

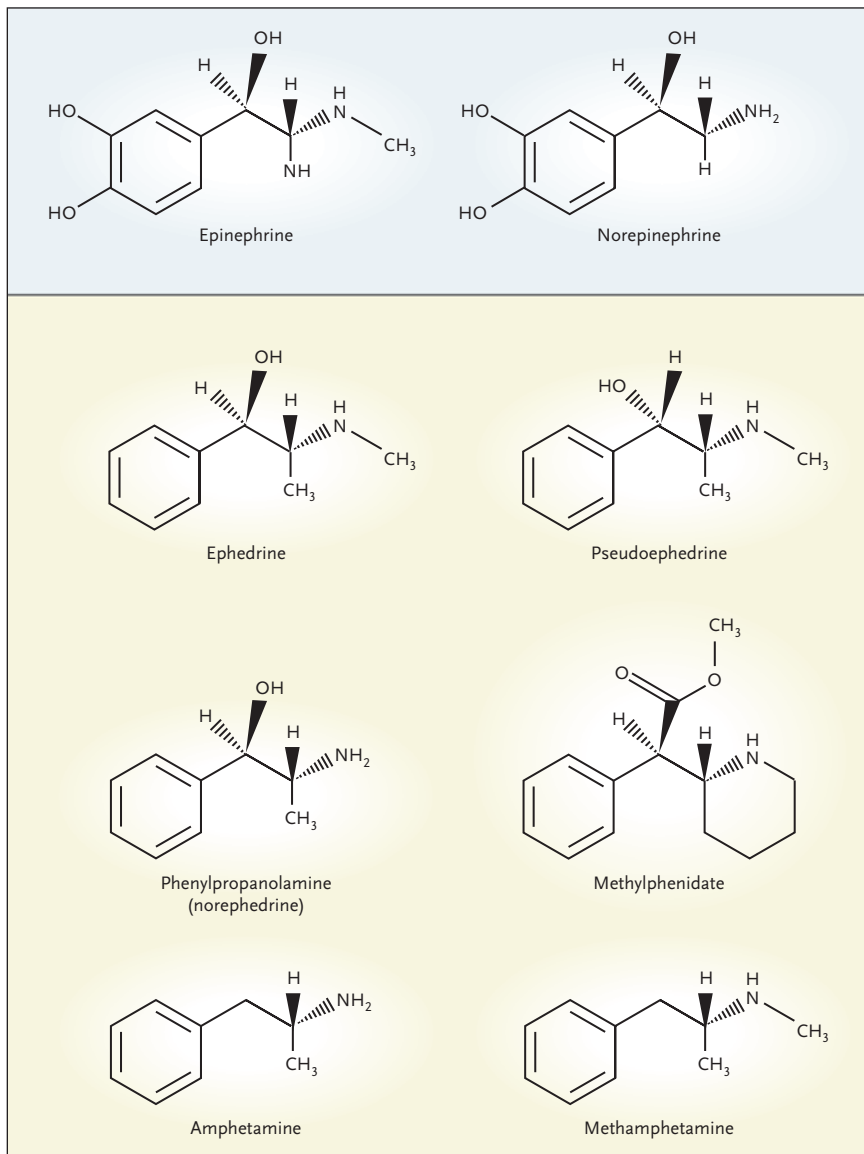
box” warning describing the cardiovascular risks of stimulant drugs used to treat attention deficit-hyperactivity disorder (ADHD). This action was unexpected, largely because the FDA had not requested a review of current labeling for this class of drugs; it had merely asked for recommendations of approaches to studying the cardiovascular risks associated with these drugs. The committee, however, decided to take an independent course. As a consultant to this committee, I introduced two motions, one recommending the black-box warning and the other proposing the development of a guide for patients, which was

approved by a vote of 15 to 0. The guides are handouts that are required to be provided at the time prescriptions are dispensed; they contain information, written in nontechnical language, about the potential hazards of the medication.

The drugs under review were primarily amphetamines (Adderall and other brands) and methylphenidate (Ritalin, Concerta, and other brands). These agents are closely related members of the class of sympathomimetic amines, the structures of several of which are shown in the diagram. These compounds exert potent stimulant effects on the cardiovascular and

central nervous systems. One of the oldest such agents, methamphetamine, was originally synthesized in 1891 and first widely used during World War II in Nazi Germany to enhance the ability of Luftwaffe pilots to stay alert during extended hours of combat. Medical use of this agent is now limited, but illicit use has grown rapidly and now represents an increasing public health problem. When smoked or injected intravenously, methamphetamine (“speed”) is associated with hyperthermia, rhabdomyolysis, myocardial infarction, stroke, and sudden death — effects well known to coroners in regions of the United States where abuse is common. Beginning in the 1950s, the stereoisomer dextroamphetamine and related agents were introduced as appetite suppressants.

ADHD is a disorder common-



Molecular Structures of Sympathomimetic Amines.

ly diagnosed in school-age boys (less commonly in girls) and is characterized by increased activity, an inability to concentrate, and poor school performance. The effectiveness of stimulants in treating ADHD has been well documented in randomized clinical trials. Amphetamines and amphetamine-like stimulants were introduced to treat ADHD in the 1950s, but the frequency of this diag-

nosis and the use of stimulants to treat it have accelerated enormously in recent years. The FDA advisory committee heard testimony indicating that 2.5 million children now take stimulants for ADHD, including nearly 10 percent of all 10-year-old boys in the United States.¹ The committee also learned that the use of these agents is much less prevalent in European countries, where the diagnosis

of ADHD is relatively uncommon. Even more strikingly, 1.5 million adults now take such stimulants on a daily basis, with 10 percent of users older than 50 years of age. The diagnosis of “adult” ADHD is a relatively recent phenomenon and has resulted in the most rapid growth in the use of such agents.¹

The concern of the advisory committee reflected several considerations. The cardiovascular effects of the sympathomimetic amines have been thoroughly described in the medical literature. These agents substantially increase the heart rate and blood pressure. In a placebo-controlled trial, mixed amphetamine salts (Adderall) administered to adults increased systolic blood pressure by about 5 mm Hg; similar effects were found with methylphenidate formulations.² Blood-pressure changes of this magnitude, particularly during long-term therapy, are known to increase morbidity and mortality. In 2005, a separate FDA advisory committee that I chaired concluded that blood-pressure changes represented such a reliable predictor of cardiovascular outcomes that class labeling would be appropriate in most cases.³ The increases in heart rate induced by sympathomimetic agents also have well-described adverse cardiovascular effects. The administration of these drugs produces persistent increases in heart rate, inducing chronic heart failure in animal models of dilated cardiomyopathy.

A review of the regulatory history of this class of drugs also helps to explain why the advisory committee took decisive action. The dietary supplement ephedra, sometimes called ma huang, contains two alkaloids, ephedrine

Cases of Sudden Death Reported to the FDA Advisory Committee from the AERS Database.*				
Patients	Amphetamines		Methylphenidate	
	Unadjudicated Sudden Deaths	Cases Meeting WHO Criteria for Sudden Death	Unadjudicated Sudden Deaths	Cases Meeting WHO Criteria for Sudden Death
		<i>number</i>		
Age, 1–18 yr		12		7
Age, >18 yr		5		1
Total	28	17	16	8

* Data are from the Adverse Event Reporting System (AERS) of the Food and Drug Administration (FDA).¹ Amphetamines include mixed amphetamine salts (Adderall), amphetamine, biphentamine, and dextroamphetamine. WHO denotes World Health Organization.

(see diagram) and its enantiomer, pseudoephedrine. These supplements have been used by millions of Americans to assist in weight loss or to increase energy. Some athletes have advocated the use of ephedra-containing dietary supplements as performance-enhancing agents. On December 31, 2003, federal officials announced plans to ban ephedra immediately. Health and Human Services Secretary Tommy Thompson told reporters, “The time to stop using these products is now.” This action followed several high-profile catastrophic outcomes linked to ephedra products, including the death of 23-year-old Baltimore Orioles pitcher Steve Bechler. Published studies reported that sales of ephedra-containing supplements represented less than 1 percent of all dietary-supplement sales but that these products accounted for 64 percent of the serious adverse reactions to supplements reported to the Centers for Disease Control and Prevention.⁴ Unfortunately, in April 2005, a federal court in Utah struck down the federal ban on ephedra. Many companies that make these products are located in Utah.

Similar regulatory actions have been proposed for phenylpropanolamine (PPA), another closely related sympathomimetic amine (see diagram). On December 22, 2005, the FDA issued a notice of “proposed rulemaking for over-the-counter nasal decongestant and weight control products” containing PPA. The notice called for a public comment period until March 22, 2006, after which the FDA would undertake regulatory action that would probably include banning the use of the agent in over-the-counter preparations. The FDA’s action followed many years of concern about the potential of PPA products to cause hemorrhagic stroke. Six years ago, a case-control study published in the *Journal* reported a 16-fold increase in the risk of stroke among women taking PPA for appetite suppression.⁵

Briefing documents prepared for the February 9 advisory-committee meeting described cases of myocardial infarction, stroke, and sudden death in children and adults taking ADHD stimulants.¹ These narratives were derived from the FDA’s Adverse Event Reporting System (AERS), a database

containing reports of adverse events submitted by health care providers. The AERS is a voluntary reporting system that has been criticized because only 1 to 10 percent of serious adverse events are actually reported, limiting the database’s usefulness for identifying emerging drug hazards. The drug-related events reviewed by the committee included 25 cases of sudden death in children or adults (see table), some with evidence on autopsy of undiagnosed congenital heart disease, such as hypertrophic obstructive cardiomyopathy. The physiology of this condition renders patients particularly vulnerable to the adverse effects of sympathomimetic drugs, because such agents increase contractility, thereby increasing the pressure gradient in the left ventricular outflow tract. Many additional cases of major adverse cardiovascular events, including myocardial infarction, stroke, and serious arrhythmias, were reviewed by the committee. However, the documentation of cases was frequently incomplete, and neither the FDA reviewers nor the committee considered the AERS data to be definitive.

Despite the difficulty of interpreting these data, the advisory committee acted preemptively to recommend strong regulatory action. The majority of the group accepted my argument that the propensity of sympathomimetic agents to raise blood pressure and heart rate, the history of serious adverse effects associated with two members of the class (ephedra and PPA), and the rapid increase in exposure, particularly among adults, warranted strong and immediate action. Although the committee recognized that there are important potential benefits of these drugs for certain highly dysfunctional chil-

dren, we rejected the notion that the administration of potent sympathomimetic agents to millions of Americans is appropriate. We sought to emphasize more selective and restricted use, while increasing awareness of potential hazards. We argued that the FDA should act soon, and decisively.

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An interview with Dr. Nissen can be heard at www.nejm.org.

Dr. Nissen is the interim chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic, Cleveland, and was a consultant to the FDA's Drug Safety and Risk Management Advisory Committee for the hearings on ADHD drugs.

1. Food and Drug Administration. Drug Safety and Risk Management Advisory Committee Meeting, February 9 and 10, 2006: table of contents. (Accessed March 16, 2006, at http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4202_00_TOC.htm.)

2. 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.

3. Nissen SE, Cardiovascular and Renal Drugs Advisory Committee. Report from the Cardiovascular and Renal Drugs Advisory Committee: US Food and Drug Administration: June 15-16, 2005: Gaithersburg, Md. *Circulation* 2005;112:2043-6.

4. Kingston RL, Borron SW. The relative safety of ephedra compared with other herbal products. *Ann Intern Med* 2003;139:385.

5. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000;343:1826-32.

The Changing Face of Teenage Drug Abuse — The Trend toward Prescription Drugs

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When Eric, an 18-year-old who lives in San Francisco, wants to get some Vicodin (hydrocodone-acetaminophen), it's a simple matter. "I can get prescription drugs from different places and don't ever have to see a doctor," he explained. "I have friends whose parents are pill addicts, and we 'borrow' from them. Other times I have friends who have ailments who get lots of pills and sell them for cheap. As long as prescription pills are taken right, they're much safer than street drugs."

Eric's habits reflect an emerging pattern in drug use by teenagers: illicit street drugs such as "ecstasy" (3,4-methylenedioxymethamphetamine) and cocaine are decreasing in popularity, whereas the nonmedical use of certain prescription drugs is on the rise. These findings were reported in

the Monitoring the Future survey, which is sponsored by the National Institute on Drug Abuse and designed and conducted by researchers at the University of Michigan.¹ The study, which began in 1975,

"We're living in a time that seems decidedly more apocalyptic. . . . Maybe we need something to slow down."

annually surveys a nationally representative sample of about 50,000 students in 400 public and private secondary schools in the United States.

Overall, the proportion of teens

who reported having used any illicit drug during the previous year has dropped by more than a third among 8th graders and by about 10 percent among 12th graders since the peaks reported in the mid-to-late 1990s, according to the 2005 survey. Alcohol use and cigarette smoking among teens are now at historic lows. In contrast, the number of high-school students who are abusing prescription pain relievers such as oxycodone (OxyContin), a potent and highly addictive opiate, or sedatives is on the rise. A total of 7.2 percent of high-school seniors reported nonmedical use of sedatives in 2005, up from a low of 2.8 percent in 1992 (see graph). Reported use of oxycodone in this group increased from 4.0 percent in 2002 to 5.5 percent in 2005.

The survey did not ask teenag-

CORRECTION

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To the Editor: Nissen (April 6 issue)¹ 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.²

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.^{3,4,5} 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.

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References

1. Nissen SE. ADHD drugs and cardiovascular risk. *N Engl J Med* 2006;354:1445-1448.
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;56:1073-1086.
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.¹ 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^{2,3} (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.

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.³

† Data are from the FDA.¹

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References

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,¹ 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.

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References

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.¹

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.² 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.² 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.³ 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.⁴

Both letters seem to ignore a fundamental fact that increasing heart rate and blood pressure⁵ 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.

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References

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.)
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;284:3036-3039.
4. Mosholder AD, Pamer CA. Postmarketing surveillance of suicidal adverse events with pediatric use of antidepressants. *J Child Adolesc Psychopharmacol* 2006;16:33-36.
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;66:253-259.