Stimulants and Sudden Death: What Is a Physician to Do?
Timothy E. Wilens, Jefferson B. Prince, Thomas J. Spencer and Joseph Biederman

Pediatrics 2006;118;1215-1219
DOI: 10.1542/peds.2006-0942

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.pediatrics.org/cgi/content/full/118/3/1215
Stimulants and Sudden Death: What Is a Physician to Do?

Timothy E. Wilens, MD*, Jefferson B. Prince, MD**, Thomas J. Spencer, MD*, Joseph Biederman, MD*

*Clinical Research Program in Pediatric Psychopharmacology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; **Department of Child Psychiatry, North Shore Medical Center, Salem, Massachusetts

Financial Disclosure: Dr Wilens receives research support from Alza Corporations/Ortho-McNeil, Eli Lilly, the National Institute on Drug Abuse (NIDA), Neurosearch, and Shire Laboratories. He is on the speaker’s bureau of Ortho-McNeil, Novartis Pharmaceuticals, and Shire Laboratories, and a consultant for Abbott, Glaxo/SKB, Janssen-Pharmaceutica, the NIDA, the National Institute on Mental Health (NIMH), Pfizer, Saegis Pharmaceuticals, and Sanofi-Synthelabo. Dr Spencer receives research support from Shire Laboratories, Eli Lilly, Novartis Pharmaceutical, Wyeth Ayerst, and McNeil Consumer and Specialty Pharmaceuticals, and is on the advisory board for Shire Laboratories, Eli Lilly, Glaxo/SKB, Pfizer, McNeil Consumer and Specialty Pharmaceuticals, and Novartis Pharmaceuticals. Dr Prince in the last 12 months has received honorarium from Cephalon, Shire Laboratories, PsychCME, Vital Issues in Medicine, and McNeil Consumer and Specialty Pharmaceuticals. He is on the speaker’s bureau for McNeil Consumer and Specialty Pharmaceuticals. Dr Biederman receives research support from Shire Laboratories, Eli Lilly, Pfizer, McNeil Consumer and Specialty Pharmaceuticals, Abbott, Bristol-Myers-Squibb, New River Pharmaceuticals, Cephalon, Janssen Pharmaceutica, Neurosearch, Stanley Medical Institute, Novartis Pharmaceuticals, Lilly Foundation, Prechter Foundation, the NIMH, the National Institute of Child Health and Human Development, and the NIDA. He is on the speaker’s bureau for Shire Laboratories, Eli Lilly, McNeil Consumer and Specialty Pharmaceuticals, Cephalon, UCB Pharma, and Novartis. He is on the advisory board for Eli Lilly, Shire Laboratories, McNeil Consumer and Specialty Pharmaceuticals, Janssen Pharmaceutica, Novartis Pharmaceuticals, and Cephalon.

ABSTRACT

OBJECTIVE. Recently, a US Food and Drug Administration advisory committee raised concerns about cardiovascular risks and sudden death in children and adolescents with attention-deficit/hyperactivity disorder who are receiving stimulants.

METHODS. We comment on the risk of sudden death in children/adolescents taking stimulants compared with population rates, biological plausibility, and known cardiovascular effects of stimulants to determine specific risk.

RESULTS. There does not seem to be higher risk of sudden death in stimulant-treated individuals compared with the general population. Although there is evidence of biological plausibility, the known effects of the stimulants on cardiovascular electrophysiology and vital signs seem to be benign.

CONCLUSIONS. There does not seem to be compelling findings of a medication-specific risk necessitating changes in our stimulant treatment of children and adolescents with attention-deficit/hyperactivity disorder. The use of existing guidelines on the use of stimulants (and psychotropic agents) may identify children, adolescents, and adults who are vulnerable to sudden death.

www.pediatrics.org/cgi/doi/10.1542/peds.2006-0942
doi:10.1542/peds.2006-0942

Key Words
ADHD, attention-deficit/hyperactivity disorder, methylphenidate, amphetamine, sudden death, cardiovascular, blood pressure, pulse, electrophysiology

Abbreviations
ADHD—attention-deficit/hyperactivity disorder
FDA—US Food and Drug Administration
SD—sudden death

Accepted for publication May 3, 2006
Address correspondence to Timothy E. Wilens, MD, YAW 6A, Massachusetts General Hospital, 55 Parkman St, Boston, MA 02114. E-mail: twilens@partners.org
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is the most common neurobehavioral disorder presenting for treatment in youth in the United States, with 3% to 9% of youth affected. Among available treatment modalities for ADHD, pharmacotherapy is considered one of the fundamental treatments for this disorder. Within the medication armamentarium for ADHD, stimulants (methylphenidate and amphetamine) are the most widely used and continue to be considered first-line agents. As highlighted in recent US Food and Drug Administration (FDA) advisory committee recommendations and editorials, lingering concerns remain regarding the potential cardiovascular safety of psycho-stimulants despite the well-documented data demonstrating their short- and long-term efficacy in the treatment of ADHD. The recently convened FDA pediatric advisory board recommended by a 15-to-0 vote that an informational booklet detailing the risk, benefits, and adverse effects of the stimulant medications be developed for parents, families, and providers. This controversy has been highlighted by the recent removal and subsequent reinstatement of extended-release mixed amphetamine salts in Canada (2005), added warnings of administration of mixed amphetamine salts in patients with preexisting structural cardiac effects, and the recent 8-to-7 vote by the FDA advisory panel recommending a “black-box” warning on the risk for sudden death (SD) in individuals receiving any stimulant (February 2006), which was not supported by another subsequent FDA advisory panel (March 2006). This state of affairs has left the field and the public in a state of high anxiety, making a reasonable approach to the care of patients with ADHD, in whom stimulants are being considered, difficult.

In considering the critical issue of SD, physicians, parents, and policy makers need to evaluate the evidence at hand. Specifically, we need to know first whether there is evidence of causality. This consideration involves estimating whether the risk of SD in individuals treated with stimulants exceeds that of the spontaneous risk for SD in the general population. Second, we need to assess the evidence for biological plausibility that treatment with stimulants produces dangerous cardiovascular outcomes. Against this background, clinicians should factor in the severity of the natural course of ADHD for which treatment with stimulants is being considered.

STIMULANT USE AND RISK OF SD

What Is the Evidence That Stimulants Increase the Risk for SD?

Although tragic, SD occurs at a rare but stable rate in the general population. Estimates indicate that the risk for SD in children and adolescents is between 0.6 and 6 in 100,000 per year. SD increases with age, with the risk in children reaching upward of 1 in 1000 per year. Of interest, the risk for SD in juvenile and adult athletes is higher, with SD occurring typically during the peak exercise or immediate postexercise periods. SD is presumed to be of cardiac origin in half of the cases, with structural heart defects (eg, idiopathic hypertrophic subaortic stenosis) accounting for the majority of abnormalities identified, followed by anomalous origin of cardiac vessels and aortic dissection and rupture. Although some retrospective data suggest that 50% of the individuals with SD had symptoms preexisting the catastrophic event including syncope, palpitations, chest pain, or dizziness; other studies have suggested that the vast majority of patients present with SD as their first and only symptom. Thus, prospective identification of these risks may reduce SD rates in the general population. Critical in the evaluation of SD risk associated with treatment with stimulants is the comparison of risk in similarly aged individuals in the general population.

As an important qualifier, many of the numbers used for calculation are approximations based on assumptions, use data, and spontaneous report. Data collected over the period of 1999–2003 indicate that, using the World Health Organization classification, there have been 25 reports of SD in patients treated with stimulants: 8 of them while on methylphenidate (7 pediatric and 1 adult) and 17 of them while on amphetamine (12 pediatric and 5 adults). The adjusted rates per million prescriptions over this period for pediatric subjects was calculated to be 0.16 for methylphenidate and 0.36 for amphetamines; rates in adults were 0.07 for methylphenidate and 0.53 for amphetamine. Because of the very rare occurrences, no meaningful comparison could be made between amphetamine- and methylphenidate-associated SD.

In comparing the risk for SD in stimulant-treated children and adolescents, the FDA Psychopharmacology Pediatric Advisory Board during their meeting on March 22, 2006, concluded that the stimulant medications do not pose an undue cardiovascular risk in children and adolescents. A review in stimulant-treated adults is still pending; however, a previous FDA review of the cardiovascular risk associated with the use of amphetamine in children and adults did not find undue risk other than increased risk in patients with underlying heart defects (www.fda.gov/cder/drug/advisory/adderall.htm).

Another line of evidence to examine in establishing a true link between stimulants and SD is the pathophysiological correlates of the SD. A majority of patients suffering SD during treatment with stimulants had autopsies. A structural cardiac defect was identified in 8 of 12 cases of SD during treatment with amphetamine and 4 of 7 that occurred during treatment with methylphenidate. These defects included a variety of cardiac abnormalities, with hypertrophic cardiomyopathies reported most commonly. It is important to note that autopsy evidence of cardiac anomalies requires special procedures that are not always performed, such as fine serial sectioning of
the myocardium. Therefore, the usefulness of a “negative” autopsy depends on the quality of the procedure. Nevertheless, the risk and distribution of the cardiac dysfunction and structural abnormalities reported in patients receiving stimulants are strikingly similar to the characteristics of SD reported in the general population: half of the cases of SD in the general population were found to have structural cardiac defects at autopsy. What remains missing from many of the cases are the specifics of the SD reports, such as timing and potential confounds of coadministered agents (prescribed, illicit, or over-the-counter), actual doses and blood levels of medications taken, concurrent illnesses, metabolic abnormalities, preexisting cardiovascular symptoms, exercise proximity, and other issues that may contribute to SD.

**What Is the Evidence That Stimulants Are Associated With Severe Cardiovascular Risk?**

A growing body of work exists about the short- and long-term effects of stimulant treatment on cardiovascular parameters in children, adolescents, and adults with ADHD who are receiving stimulants. These data, limited to healthy subjects without known preexisting cardiac anomalies, consistently demonstrate small, statistically significant, but not clinically meaningful increases in blood pressure and pulse as well as minimal changes during electrocardiography. For example, recent multisite pediatric studies with methylphenidate and amphetamine that included >2000 children documented mild, statistically significant increases in both systolic (2–4 mm Hg) and diastolic (1–3 mm Hg) blood pressure and heart rate (3–5 beats per minute) that persisted at the same magnitude with continued treatment to 2 years. During the March 22, 2006, meeting of the FDA Pediatric Psychopharmacology Advisory Panel, investigators for the ongoing Multimodal Treatment of ADHD follow-up protocol reported (over 6 years of follow-up) no differences in blood pressure or pulse between those treated with medication and those not treated with medications. Short-term 24-hour ambulatory blood pressure monitoring has also shown similar findings. In both short and longer-term studies, there were low drop-out rates secondary to abnormal cardiovascular parameters and <1% of medically healthy children and adolescents noted to have isolated systolic or diastolic hypertension (eg, >90th percentile for age) or clinical symptoms referable to cardiovascular symptoms (eg, chest discomfort, syncope, palpitations). Studies of adults reflect those of children and adolescents, although, not surprisingly, higher rates of hypertension have been observed because blood pressure naturally increases with age. Higher drop-out rates, resulting from exceeding the normal blood pressure cut-offs, in clinical trials has been observed in adults relative to children, although dropouts are also observed in the placebo groups (eg, natural occurrence of hypertension).

One consideration in determining potential causality is biological plausibility; in other words, is there some inherent physiochemical characteristic of the medication that may predispose someone to an adverse physiologic response? The stimulant medications are catecholaminergic (noradrenergic and dopaminergic) and have sympathomimetic qualities. Catecholaminergic agents, theoretically, can affect the rate, cardiac conduction, and repolarization and rhythmicity of the heart. However, not all catecholaminergic agents are alike; for instance, isoproterenol has substantial effects on all aspects of cardiac electrophysiology, whereas the stimulants used to treat ADHD have a significantly milder effect.

The stimulant medications have both chronotropic (heart rate) and ionotropic (contractility) effects. Electrocardiographic effects of stimulants include predictable increases of heart rate that are rarely in the range of diagnosed tachycardia (140 beats per minute in children and 120 beats per minute in adolescents). Studies indicate no changes in the PR (atrial conduction), QRS (intraventricular conduction), or QT/QTc intervals (repolarization). Studies in adults reflect those in children, with no known changes in atrial or ventricular conduction or repolarization in clinical trials. In all of the studies of stimulants in children, adolescents, and adults (>300 controlled trials; N > 5000 children and adolescents) of various length, to our knowledge, there has been no SD reported.

**SUMMARY**

Given the existing data, the rates of SD in children, adolescents, and adults who are treated with stimulants are exceedingly rare. Furthermore, it remains very unclear whether the risk for SD is actually higher in patients receiving stimulants than in the general population. Moreover, the anatomic characteristics identified on autopsy of patients suffering SD during treatment with stimulant medications are similar to those reported in SD in the general population. Therefore, without a specific association, there is no causality.

Conceptually, stimulants have a theoretical biological plausibility to set a cascade of events that may result in SD. However, the stimulants’ relatively benign effects coupled with the lack of electrocardiographic changes (in some cases being more benign than over-the-counter and other treatments) do not seem to be sufficient to result independently in SD. Whether the stimulants interact with “vulnerable” patients such as those with presumed preexisting cardiac disease to create rhythm disturbances remains unclear, and if these disturbances are operant, they are probably occurring at an extremely low baseline rate. At the meeting on March 22, 2006, the FDA Pediatric Psychopharmacology Advisory Panel concluded that there was no evidence of increased risk of SD.
in healthy children with ADHD who are treated with stimulant medication. Moreover, the panel equated the putative risk of SD in children with ADHD who have preexisting structural abnormalities and are treated with stimulants to that of strenuous exercise in this population.

Balancing the Risks
The theoretical risk of using stimulants needs to be balanced against the very real risks of leaving ADHD untreated. The vast literature shows that stimulants are highly effective for ADHD. For instance, cross-sectional and longitudinal studies show that ADHD is a risk for substantial morbidity, including academic, occupational, and interpersonal failure, sexual promiscuity, criminality, and injuries. Increased risk for motor vehicle accidents, one of the leading causes of death in adolescents and young adults, has been documented in ADHD, with reversal in driving deficits with stimulant treatment. Untreated individuals with ADHD have twice the risks for cigarette smoking and early-onset substance abuse, which are independently linked to premature death in adults. Not surprisingly, stimulant treatment in those with ADHD has been shown to reduce the initiation of both cigarette smoking and substance abuse. The morbidity and mortality either directly or indirectly ascribed to ADHD or its sequela are substantial and notably reduced in the presence of stimulant treatment. Hence, the risk/benefit ratio at both a clinical and public health level underscores the consequences of undertreating ADHD or leaving it untreated.

What Cardiovascular Monitoring Should be Undertaken with Stimulant Treatment?
On the basis of the findings encompassing the most recent data available, it seems prudent to follow the established guidelines by the American Heart Association Panel on Psychotropic Agents in Children and Adolescents that previously reviewed data on the stimulants. Although stimulants were not identified as associated with SD, the panel suggested querying for independent risk factors for SD before initiating medication and during treatment, namely, family history of premature SD (<30 years) and personal history of syncope, palpitations, chest pain, or dizziness of unknown etiology, especially during exercise. Blood pressure and pulse should be examined at baseline and periodically during treatment. As reaffirmed during the FDA Pediatric Psychopharmacology Advisory Panel on March 22, 2006, other than clinical history and usual physical examination, there is no good way to screen for occult structural cardiac disease. In medically healthy children and adolescents to be administered stimulants, there is no need to complete an echocardiogram or 12-lead or Holter electrocardiograph. In those patients with the aforementioned symptoms, referral for a more thorough workup is indicated. In adults, an appropriate cardiac workup based on the risk factors of the individual is suggested.

CONCLUSIONS
The available data do not seem adequate to warrant major changes in our current treatment of ADHD with stimulants. Balanced against the paucity of convincing data on adverse cardiovascular effects of stimulants are the morbidity and mortality associated with not treating the disorder appropriately. Stimulants remain among the most effective and safe intervention for ADHD.

The application of previously developed American Heart Association guidelines devoted to the use of psychotropic agents in children and adolescents seems prudent in identifying those at risk for adverse cardiovascular outcomes independently and potentially through an interaction with these treatments. Specific unsolicited warnings directed to patients and their families about SD risk associated with stimulants seems premature given the lack of clear association and current state of knowledge. Given these findings, it would be unfortunate to create an atmosphere of unwarranted fear and deter the appropriate, medically indicated, and monitored use of stimulants for ADHD, one of the most useful treatments in child psychiatry and pediatrics over the past 5 decades.

ACKNOWLEDGMENT
The funding for this study was provided by National Institutes of Health grant K24 DA016264 (to Dr Wilens).

REFERENCES
8. Aman MG, Werry JS. Methylphenidate in children: effects...
upon cardiorespiratory function on exertion. *Int J Ment Health.*
41. Monuteaux MC, Biederman J, Spencer T. A randomized, double-blind, placebo-controlled clinical trial of bupropion for the prevention of smoking in youth with attention deficit/hyperactivity disorder. Presented at: NCI Tobacco Investigators Meeting: Synthesizing Research for the Public’s Health; San Diego, CA; June 2–4, 2004