AHA Scientific Statement

Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Medications for Attention Deficit/Hyperactivity Disorder

A Scientific Statement From the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing

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Over the past decade, concerns have been raised regarding the safety of a variety of psychotropic medications in children and adolescents, the appropriate selection of patients for therapy, and the indications for cardiovascular monitoring. In 1999, concerns over potential cardiovascular effects of psychotropic drugs, especially tricyclic antidepressants[1,2] but including stimulants, prompted the American Heart Association (AHA) scientific statement "Cardiovascular Monitoring of Children and Adolescents Receiving Psychotropic Drugs."[3] At that time, no specific cardiovascular monitoring was recommended for the use of stimulant medications. Since that time, a constellation of circumstances have come together, necessitating a second look at this complicated issue. These circumstances include an increased awareness of the presence of attention deficit/hyperactivity disorder (ADHD) in the general population and in children with preexisting cardiac conditions; public concerns about the side effects and toxicities of medications, especially psychotropic medications in children; and regulatory factors and warnings issued by the US Food and Drug Administration (FDA) and by the pharmaceutical industry in response to the FDA. This writing group was convened in response to FDA concerns with regard to the safety of the ADHD drugs and with regard to the identification of children with underlying cardiovascular abnormalities.

At a time when there is much discussion of the side effects of drugs and of the use of psychotropic drugs in children in the media and lay literature, it is particularly important for the medical profession to play a significant role in critically evaluating the use of stimulant medication in children, including those who may have undiagnosed heart disease and those who are known to have heart disease.

The writing group for "Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Medications for Attention Deficit/Hyperactivity Disorder" reviewed the literature relevant to this topic since the last publication of the AHA scientific statement that included these drugs in 1999 to assist the group in their recommendations. Literature searches were conducted in PubMed/MEDLINE databases to identify pertinent articles. The major search terms included stimulant drugs, methylphenidates, amphetamines, sudden cardiac death (SCD), death, arrhythmias, ventricular tachycardia, ADHD, attention deficit disorder, cardiovascular side effects, treatment of ADHD in children, ADHD and stimulant medications, SCD in children and adolescents, methylphenidates and cardiac death, and amphetamines and cardiac death. Searches were limited to the English language from 1980 through August 2007. In addition, related article searches were conducted in MEDLINE to find further relevant articles. The information available on the FDA Web site (www.fda.gov) regarding Advisory Committee meetings was used. Finally, committee members recommended applicable articles outside the scope of the formal searches.

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Table 1. Classification of Recommendations and Level of Evidence

Classification of recommendations
Class I: conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective and should be performed. Benefit>>>risk.
Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy. It is reasonable to perform procedure/administer treatment. Benefit>>risk. Additional studies with focused objectives needed.
Class IIb: usefulness/efficacy is less well established by evidence/opinion. Procedure/treatment may be considered. Benefit≥risk. Additional studies with broad objectives needed; additional registry data would be helpful.
Class III: conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful. Risk≥benefit. No additional studies needed. Procedure/treatment should not be performed/administered because it is not helpful and may be harmful.
Level of evidence
A: data derived from multiple randomized clinical trials or meta-analyses
B: data derived from a single randomized trial or nonrandomized studies
C: Only consensus opinion of experts, case studies, or standard of care

Using the evidence-based methodologies developed by the American College of Cardiology/AHA Task Force on Practice Guidelines, the writing group has given classifications of recommendations and levels of evidence when applicable. The classifications of recommendations and levels of evidence are shown in Table 1.

A recommendation with level of evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful and effective.

Overview of ADHD

Overview of ADHD in the General Population of Children

ADHD, the most common neurobehavioral disorder of childhood, is characterized by developmentally inappropriate levels of hyperactivity, inattention, and impulsivity. Additional defining features include impairment in executive function and behavioral self-regulation.[4–6] Prevalence rates of 4% to 12% have been reported in community-based samples of school-aged children in the United States.[7–9]

Diagnosis

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) defines 3 ADHD clinical phenotypes—inattentive, hyperactive-impulsive, and combined—based on symptom count (6 for either inattentive or hyperactive-impulsive and 6 in each category for combined) causing impairment in functioning in at least 2 settings (home, school, social).[10] Comorbidity, including oppositional defiant disorder (35%), conduct disorder (30% to 50%), anxiety disorders (25%), mood disorders (15% to 75%), and learning disabilities (25%), also has been reported in clinical samples of ADHD children and adolescents.[11–13]

Origin and Risk Factors

Investigations into the origin of ADHD have focused on the central nervous system involvement, the genetics of the disorder, and environmental risk factors.[14]

Central Nervous System Involvement

Converging evidence from neuropsychology, neuroimaging, neuropharmacology, and genetics suggests involvement of the frontostriatal dopaminergic circuits in the brain.[14]

Genetic Influence in ADHD

Family studies report a higher incidence of ADHD among first-degree family members of ADHD male and female probands.[15–18] Faraone et al[19] have estimated the heritability of ADHD at 0.76, making ADHD one of the most heritable psychiatric disorders.

Environmental Risk Factors

The concordance rate of 33% in dizygotic twins, double the rate reported in siblings,[20] points to environmental risk factors incurred during the prenatal course. Environmental factors that have been most consistently associated with ADHD include maternal smoking during pregnancy,[21,22] emotional distress or family adversity during pregnancy and early in life,[21,23,24] birth weight <1500 g,[24] hypoxemia,[25] encephalitis,[26] trauma,[27] lead exposure,[28] and brain injury from some metabolic disorders.[29]

ADHD in Children With Heart Disease

ADHD may be more prevalent in children with heart disease than in the general pediatric population. Mahle et al[30] have reported abnormal attention scores in 45% of children and abnormal hyperactivity scores in 39% of children with heart disease based on the responses of parents and teachers on the DSM-IV Rating Scale and Behavior Assessment System for Children. In this study, more than two thirds of children with hypoplastic left heart syndrome were thought to have attention/hyperactivity problems. In 2004, Kirshbom and colleagues[31] found that 50% of children with total anomalous pulmonary venous return displayed abnormal hyperactivity and/or attention deficits. As previously noted, chronic or intermittent hypoxia experienced by children with heart disease has been linked to adverse effects on development, academic achievement, and behavior.[25] Congenital cardiovascular anomalies are present in 76% of children with velocardiofacial syndrome/DiGeorge syndrome, caused by 22q11 microdeletion.[32] ADHD affects 35% to 55% of these children.[33]

Impact and Sequelae of ADHD and Risks of Not Treating

ADHD and its associated conditions have a profound impact on individuals, families, and society. Children with ADHD compared with their non-ADHD peers are at high risk for injuries, academic underachievement, and social difficulties such as peer rejection.[34–36] These difficulties often persist into adulthood. Individuals with ADHD attain lower occupational status than peers and are at increased risk of developing problems with substance use and antisocial behavior, as well as increased rates of automobile accidents.[37–39] Thus, in 1998, the National Institutes of Health consensus panel on the diagnosis and treatment of ADHD concluded that the costs associated with ADHD were large, stating that individuals with ADHD "consume a disproportionate share of resources and attention from the health care system, criminal justice system, schools, and other social service agencies."[39a]

History of the Problem Regarding Stimulant Medications

Recent Events

A review of the current concerns regarding these medications and recommendations regarding monitoring of those on medications follows.

Health Canada and Adderall XR

In February 2005, Health Canada, the Canadian drug regulatory agency, suspended the sale of Adderall XR in the Canadian market. The Canadian action was based on US postmarketing reports of sudden deaths in pediatric patients. In response to the Health Canada action, the FDA released a "Public Health Advisory for Adderall and Adderall XR," stating that it "had been aware of these post-marketing cases, and evaluated the risk of sudden death with Adderall prior to approving the drug for treatment of ADHD in adults last year."[39b] The factors potentially associated with these sudden deaths in the FDA Adverse Event Reporting System database included cardiac structural abnormalities such as aberrant origin of coronary artery, idiopathic hypertrophic subaortic stenosis, bicuspid aortic valve, and cardiac hypertrophy. Other factors listed were unexplained increased or toxic amphetamine level, family history of ventricular arrhythmia, and extreme exercise and dehydration. The FDA stated that "the number of cases of sudden deaths reported for Adderall is only slightly greater, per million prescriptions, than the number reported for methylphenidate products, which are also commonly used to treat pediatric patients with ADHD."[39b] Despite the lack of data to support limiting the use of the stimulant medications in children with heart disease, in August 2005, the FDA added a warning to the Adderall labeling, titled "Sudden Death and Preexisting Structural Cardiac Abnormalities," which states, "Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR generally should not be used in children or adults with structural cardiac abnormalities."[39c] Additionally, a boxed warning states, "Misuse of amphetamine may cause sudden death and serious cardiovascular events." Health Canada reinstated the marketing authorization of Adderall XR in Canada effective August 26, 2005, with the stipulation that the drug monograph note the same warning as above.

Other Stimulant Medications and the FDA

In June 2005, at a meeting of the FDA Pediatric Advisory Committee, postmarketing reports regarding methylphenidate products were discussed, raising concerns regarding their cardiac safety. Long-term safety trials and targeted cardiovascular risk studies were mentioned as a potential option to better understand the cardiovascular risks for all drug products approved for ADHD. A review of adverse events of all stimulant products and atomoxetine occurred in early 2006 as described below. The importance of evaluating both methylphenidates and amphetamines, given that both are stimulants, was stated by the FDA "to avoid switching from one class to the other based on incomplete safety assessments."[39d] Additionally, the FDA stated that it could not determine whether adverse cardiovascular events in patients on methylphenidate-based stimulants were "causally associated with the treatment."[39d]

On February 9, 2006, the Drug Safety and Risk Management Advisory Committee of the FDA convened to discuss how to research heart risk associated with medications.[40] Reports from that conference reflect that between 1999 and 2003, 25 people (19 children) taking ADHD medications died suddenly and 43 people (26 children) experienced cardiovascular events such as strokes, cardiac arrest, and heart palpitations.[40] The FDA advisory panel recommended with an 8-to-7 vote that a "black box" warning about possible cardiovascular risks associated with stimulant medications used to treat ADHD be added to the drug labeling. Furthermore, it was recommended that clinicians continue to follow American Academy of Pediatrics guidelines on the assessment and management of ADHD.

The FDA Pediatric Advisory Committee met in March 2006 to review the reports of heart and psychiatric problems associated with ADHD medications.[41] Additional data in children from 1992 to February 2005 revealed 11 sudden deaths associated with methylphenidates and 13 associated with amphetamines. Additionally, 3 sudden deaths were reported in children on atomoxetine between 2003 and 2005.[41] The Pediatric Advisory Committee did not follow the prior Drug Safety Committee's recommendations for a black box warning but suggested that this drug information be placed in the "highlights" section of the newly formatted labeling (January 2006) with warnings that "children with structural heart defects, cardiomyopathy, or heart-rhythm disturbances may be at risk for adverse cardiac events, including sudden death." Additionally, the Pediatric Advisory Committee recommended that an informational booklet describing the risks, benefits, and adverse effects of the stimulant medications be developed for parents, families, and providers.

In a recent editorial, concerns were raised about the cardiovascular risks of stimulant drugs used to treat ADHD, supporting a black box warning,[42] with subsequent responses and articles suggesting a more tempered view with a weighing of risks and benefits to these children.[43,44] Review of the available data suggests that some of the children who died may have had the specific types of cardiac lesions that predispose to SCD. Others who died were not known to have any of these risk factors, but few data are available because these data were provided voluntarily through the FDA Adverse Event Reporting System by a variety of reporters, including parents, doctors, coroners, pharmacists, other health professionals, and media reporters, resulting in possible underreporting or limited reports. Reports of arrhythmias and sudden unexpected death associated with amphetamines are primarily case reports, FDA self-reports with little information, or reports of abuse of amphetamines.[45,46] There are no systematically collected data to indicate that "structural heart disease" broadly should be a reason to avoid these medications. Likewise, there are no data to identify the actual risks of stimulant medication in children with congenital heart disease. At the present time, a few epidemiological studies are in progress, but no studies are specifically focused on identifying precise cardiac diagnoses of concern in children with ADHD and exposure to stimulant medications.

On February 21, 2007, the FDA issued a press release titled "FDA Directs ADHD Drug Manufacturers to Notify Patients About Cardiovascular Adverse Events and Psychiatric Adverse Events."[46a] The press release indicated that "the US Food and Drug Administration (FDA) today directed the manufacturers of all drug products approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) to develop Patient Medication Guides to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medicines, and to advise them of precautions that can be taken." Additionally, the FDA recommended "that children, adolescents, or adults who are being considered for treatment with ADHD drug products work with their physician or other health care professional to develop a treatment plan that includes a careful health history and evaluation of current status, particularly for cardiovascular and psychiatric problems (including assessment for a family history of such problems)." These patient medication guidelines have been developed for 15 medications, including all of the stimulant medications used for ADHD such as amphetamines, methylphenidates, and atomoxetine. All mention the risk of sudden death in patients who have heart problems or heart defects. In the medication guide section titled "Who Should Not Take (Name of Drug),"[46b] the amphetamine medication guides indicate regarding cardiovascular effects that (name of drug) "should not be taken if you or your child has heart disease or hardening of the arteries or moderate to severe high blood pressure." Further in the section titled "(Name of Drug) May Not Be Right for You or Your Child," the guide instructs that before (name of drug) is started, "tell your or your child's doctor about all health conditions (or a family history of), including: heart problems, heart defects, high blood pressure." Additional concerns about other noncardiovascular issues are listed in all of the medication guides.

The medication guide for the methylphenidate products includes general information about sudden death and heart problems or heart defects but does not state that individuals with heart disease should not take the product. Rather, the guide includes this information in the section titled "(Name of Drug) May Not Be Right for You or Your Child." It instructs, "Before starting (Name of Drug) tell your or your child's doctor about all health conditions (or a family history of) including: heart problems, heart defects, high blood pressure."

The atomoxetine medication guide uses wording and placement of the warning about heart problems similar to those of the methylphenidate medication guides. All of these medication guides can be found on the FDA Web site.[46b]

The drug labels in the specific monographs are similar, and most have a statement that indicates that these "stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug." A few of the labels focus more on hypertension, heart failure, and myocardial infarction, in addition to cardiac arrhythmias.

Risk of SCD in Children

Epidemiology

It is estimated that SCD claims the lives of 1000 to 7000 children and adolescents each year in the United States, accounting for ≈5% to 10% of all childhood deaths annually, with an incidence of 0.8 to 6.2 per 100 000.[47] The exact number is not entirely clear. Clinical experience suggests that SCD can occur not only in the setting of organized sports but also in children and adolescents engaged in many levels of activity or even in the absence of activity. In children and adolescents, SCD usually is associated with cardiomyopathy, primary electrical disease, or congenital heart disease, reflecting the fact that an underlying substrate must be present to place a child or adolescent at risk.

Cause

The most common causes of SCD in the United States are hypertrophic cardiomyopathy (HCM; 33% to 50%); long-QT syndrome (LQTS; 15% to 25%); other cardiomyopathies, including arrhythmogenic right ventricular dysplasia and dilated cardiomyopathy (10% to 20%); coronary artery anomalies (10% to 20%); primary ventricular fibrillation or tachycardia (10% to 15%); Wolff-Parkinson-White syndrome (WPW; 3% to 5%); and others, including aortic rupture (5%).[48] HCM has a prevalence of 1 in 500 in the United States, with an incidence of sudden death in children of 2% to 8% per year.[49–51] A 12-lead ECG is abnormal in 75% to 95% of patients with HCM.[52] In LQTS, 4000 cases of SCD in children and adults in the United States occur each year, often as a result of adrenergic stimulation leading to triggering of ventricular arrhythmias, including the characteristic torsades de pointes, a form of ventricular tachycardia.[53] ECG abnormalities are present in 90% of LQTS patients and include prolongation of the corrected QT interval (QTc) with abnormal T-wave morphology. Brugada syndrome, with a prevalence of 1 to 5 in 10 000 in the Western countries, is characterized by findings of right bundle-branch block and ST-segment elevation in the precordial leads and syncope or aborted SCD; the risk of ventricular fibrillation or SCD over a 3-year follow-up period was shown to be 40%.[54] WPW syndrome is the most common form of ventricular preexcitation with a prevalence of the WPW pattern on ECG of 1 to 3 in 1000. WPW can result in SCD because of rapid conduction of atrial fibrillation down the accessory pathway resulting in ventricular fibrillation.[55] Other causes of SCD include congenital anomalies of the coronary arteries, arrhythmogenic right ventricular dysplasia, other cardiomyopathies and myocarditis, Marfan syndrome, short-QT syndrome, commotio cordis, and pulmonary hypertension.

Table 2. Arrhythmia and Sudden Death Incidence Associated With Postoperative Congenital Heart Defects

Lesion	Arrhythmia Incidence, %	Sudden Death Incidence, %	Common Arrhythmias
d-TGA, intra-atrial repair	50–85	8	AF, SSS
d-TGA, arterial switch repair	3–4	1	VT/VF, EAT
Tetralogy of Fallot	30–60	2–6	VT, AF
S/P Fontan (SV, HLHS, TA)	25–40	3–5	AF, SSS, VA, EAT
Aortic stenosis	10	5–10	VA, VT
VSD, AV canal defects	10	2–4	VA, VT, AVB

d-TGA indicates d-transposition of the great arteries; AF, atrial flutter; SSS, sick sinus syndrome; VT, ventricular tachycardia; VF, ventricular fibrillation; EAT, ectopic atrial tachycardia; SV, single ventricle; HLHS, hypoplastic left heart syndrome; TA, tricuspid atresia; VA, ventricular arrhythmias; VSD, ventricular septal defect; AV, atrioventricular; and AVB, AV block.

Risks of Arrhythmia and SCD in Children With Operated Congenital Heart Disease

All patients who undergo cardiac surgery are at risk for developing cardiac arrhythmias.[56] The correction of specific defects predisposes the patient to the development of specific types of abnormal cardiac rhythms, which include supraventricular tachycardia, atrial flutter or fibrillation, ectopic atrial tachycardia, sick sinus syndrome, ventricular tachycardia, atrioventricular block, and sudden death. Cardiac arrhythmias result in significant morbidity in these congenital heart disease patients with an incidence of sudden death of 2% to 10%. The incidence of postoperative arrhythmias varies from 3% to 85% (Table 2).[57]

Prevention of SCD

Secondary Prevention

Regardless of the initial cause, the event leading to SCD in children and adolescents is increasingly recognized to involve unstable ventricular rhythms; the only life-saving treatment is rapid defibrillation.[58] For each minute that passes without defibrillation, survival decreases 10%. After the deaths of several high profile athletes and schoolchildren in many communities in recent years, both private programs and legislation have been initiated to provide for automated external defibrillators in public places, including school systems. Studies demonstrating ease of use have shown that trained sixth graders are able to operate the device correctly.[59] When defibrillators are more readily available, time to defibrillation may be reduced and survival rates improved.

Primary Prevention

Although rapid defibrillation may be an effective treatment for many children, it is still unclear how best to identify those children at risk for SCD through primary screening.[60] Identification would allow early intervention to decrease the risk of SCD.

Universal ECG Screening

ECG screening on a large scale has been implemented successfully in other countries.

ECG Screening in Japan

Since 1973, mass screening of schoolchildren for cardiovascular disease has been mandatory in Japan.[61] The greater sensitivity of ECG screening compared with history and physical examination has been documented in studies of Japanese schoolchildren. In a study of ≈120 000 schoolchildren from 1980 to 1984, cardiovascular disease was detected in 78 children. ECG was more sensitive than history or physical examination in identifying abnormalities.[62] In another study from 1994 to 1996, 0.1% of Japanese schoolchildren (100 of 92 000) were identified as having WPW.[63]

ECG Screening of Athletes in Italy and Europe

In Italy, screening of all athletes participating in organized sports has been mandated for >30 years by the Italian government under the Medical Protection of Athletic Activities Act. From 1979 to 1996, 33 735 athletes <35 years of age were screened. A total of 621 athletes were disqualified from competition because of cardiovascular conditions, including 22 athletes with HCM.[64] Interestingly, in 1998, the rate of SCD resulting from HCM was reported to be lower in Italy than in the United States, although the overall incidence was the same.[64] In the Italian preparticipation study, the ECG had a 77% greater power to detect HCM than the history and physical examination alone.[64] Recent publications from the Italian athletic preparticipation program indicate that the incidence of SCD in athletes, especially resulting from cardiomyopathies, has significantly decreased. Evaluation of 42 386 athletes between 1979 and 2004 (12 to 35 years of age) who underwent the Italian screening (ECG, examination, and echocardiogram if the ECG or examination was abnormal) showed that the annual incidence of SCD in athletes decreased by 89% (from 3.6 to 0.4 in 1000 person-years). Only 2% of athletes were disqualified.[65]

Another study looked at the efficacy of the screening program in identifying HCM by performing echocardiograms on 4450 athletes who were designated as normal and qualified to participate in athletic activities a mean of 5 months after the qualifying screening. The echocardiogram was normal in this group who had been cleared by ECG and examination 98.8% of the time.[66]

A 2005 consensus statement from the European Society of Cardiology on cardiovascular preparticipation screening of young competitive athletes recommends a common European screening program for young athletes based on the 12-lead ECG.[67]

ECG Screening of Newborns in Italy

In addition to the screening program for athletes, Italy has recently initiated a newborn ECG screening program and has identified infants with conditions predisposing them to SCD. In 1998, a report of >33 000 neonates found that half of the 24 infants in that study who died of sudden infant death syndrome had a QTc of >0.44 seconds with 4 having intervals ≥0.46 seconds. Prolongation of the QT interval was thought to be strongly associated with sudden infant death syndrome.[68] The most recent reported data from the Italian neonatal screening program showed an incidence of prolonged QTc >0.47 seconds in 0.7% and an identified long-QT mutation in half of these.[69] Although this initial article raised a great deal of controversy, subsequent molecular genetic studies have shown that ≈10% of sudden infant death syndrome cases have functionally significant genetic variants in LQTS genes.[70]

International Olympic Committee Recommendations on Preparticipation Athletic Screening

On December 10, 2004, the International Olympic Committee Medical Commission issued a protocol for cardiovascular screening of athletes.[71] This included a personal history questionnaire, a family history questionnaire, a physical examination, and a 12-lead ECG.

Athletic Screening in the United States: Preparticipation History and Physical Examination

The preparticipation history and physical examination for those involved in athletics are the primary screening tools currently used in the United States. Despite AHA recommendations in 1996,[72] screening by history and physical examination is limited by inconsistencies in personnel and forms used across states. In 1998, a study found that 40% of states had inadequate history and physical examination screening, having no approved history and physical examination questionnaire, no formal screening requirement, or forms judged to be inadequate.[73] Screening athletes only misses the >25 million schoolchildren per year who do not participate in sports. In the portion of school student athletes screened, the type of screening is inadequate nearly half of the time. Furthermore, concerns have been raised over the low sensitivity and cost-effectiveness of the preparticipation history and physical examination.[75]

AHA Statement on Preparticipation Screening in Athletes: 2007 Update Regarding ECG Screening

In response to the recently published Italian screening studies and the European Society of Cardiology and International Olympic Committee recommendations that an ECG be included in preparticipation athletic screening, the AHA Nutrition, Physical Activity, and Metabolism Council issued a new AHA Scientific Statement.[76] This new statement, an update of the 1996 AHA preparticipation screening scientific statement, indicates that the panel "addresses the benefits and limitations of the screening process for early detection of cardiovascular abnormalities in competitive athletes, cost-effectiveness and feasibility issues, and relevant medical-legal implications." The new recommendations are virtually unchanged from the 1996 recommendations and include the 12 elements of the preparticipation screening evaluation with personal and family medical history and physical examination. Studies using these standards from the 1996 statement have shown that 17% of those surveyed included all of the elements in their preparticipation screening.[77] The European Society of Cardiology and International Olympic Committee model is noted in this AHA statement to be "a benevolent and admirable proposal deserving of serious consideration" but "impractical and not applicable" to the American system because of the financial resources, manpower, and logistics required for a national screening program. It is stated that "the panel does not arbitrarily oppose volunteer-based athlete screening programs with noninvasive testing performed selectively on a smaller scale in local communities, if well designed and prudently implemented. The use of ECG screening in professional athletes, now mandated by the NBA [National Basketball Association], is noted."

ECG Screening of Nevada High School Athletes

In a study of 5615 young athletes in Nevada, the sensitivity of the ECG in identifying serious cardiovascular abnormalities was 73% versus 4.5% for history and physical examination.[78] Specificity was comparable with the 2 screening methods at ≈95%. Concern for low specificity of ECG screening centers on the fact that many highly trained athletes develop remodeling of the left ventricle that manifests in ECG changes.[79–81] One reason for the higher specificity found in the Nevada study is that high school athletes are not as highly trained and have not had left ventricular remodeling to the extent of the Olympic and college athletes in other studies.[79] In the Nevada study, 2.3% of patients screened (130 of 5615) had ECG changes of concern for HCM. All of these patients had normal blood pressure and subsequent normal echocardiogram. They were all judged to have an "athletic heart," and none were disqualified from competition.[78] Overall, only 0.4% of high school athletes in this study (22 of 5615) were disqualified from competition, all of whom had cardiovascular abnormalities that precluded participation based on Bethesda Conference guidelines for sports participation.[82] Low specificity resulting from false positives from "athlete heart syndrome" should be even less of a concern when screening the general population of schoolchildren. Smaller studies focusing on screening athletes have detected few potentially lethal cardiovascular abnormalities. However, they have not been powered to do so, with the largest study including just over 5000 high school athletes.[78] Screening for SCD with ECG has been shown to be more sensitive than history and physical examination.

Echocardiographic Screening of Junior High Students

Interestingly, a study of 357 healthy junior high students identified previously unknown cardiac defects in 3.6% of children using echocardiographic screening.[83] Two patients required interventional cardiac catheterization, and 1 patient underwent open heart surgery. The echocardiogram was more sensitive in detecting cardiac abnormalities than a physical examination performed by a pediatrician or cardiologist; ECG data were not published in this study.

Measurement of the QT Interval and Predictive Value

The precise value of an abnormal QTc is difficult to ascertain from the literature and has evolved over time, as have the methods of measuring and correcting QT intervals. Six methods have been proposed,[84,85] and a recent article by experts in the field has suggested normal QTc values. A Bazett-corrected QT interval >460 ms on ECG was stated to be prolonged in a study of 158 children. In a recent publication, abnormal values were >450 ms for adult men, >470 ms for women, and >460 ms for 1- to 15-year-olds.[86] QTc intervals of ≥0.47 second in male subjects and ≥0.48 seconds in female subjects were completely predictive but resulted in false-negative diagnoses in 40% of the male and 20% of the female subjects in a study of carriers of long-QT genes.[87] Because there are no large population studies of QTc intervals in children at the present time correlating QTc intervals with a definitive genetic diagnosis of LQTS, the predictive value of the ECG for LQTS in the general population is not known. However, there are no data to suggest that it would not be as valuable in the child previously unknown to have LQTS as it is in the child with a definitive genetic diagnosis. Up to 15% to 20% of individuals with long-QT mutations have been shown to have normal QTc intervals on an ECG, and serial ECGs have been shown to be more diagnostic than a single ECG.[87,88]

Cost-Effectiveness of ECG Screening

ECG screening has been shown to be more cost-effective than history and physical examination, with an estimated cost of $44 000 versus $84 000 per year of life saved.[75] These data come from the Nevada study of high school athletes and include the cost of further testing necessary after identification of a possible abnormality by the initial screening test. In the Nevada study, 10% of athletes (582 of 5615) underwent an echocardiogram to further investigate abnormalities in history, physical examination, or ECG.[78] Analysis of data from the neonatal screening program in Italy indicated that this type of program was highly cost-effective, with the cost per year of life saved being 20 400 euros.[89] A published response to this article questioned the applicability of the calculations to the US medical system.[90]

Screening in the United States

Although the current literature suggests that screening for SCD with ECG may be more effective than the current system in place in the United States, a large-scale screening program has not been implemented or tested to date. Screening is being done by industry and grass roots groups but without a systematic protocol or follow-up in many instances. Some screenings include ECG, some include echocardiography, and some include both.

Pharmacotherapy of ADHD

Mechanisms of Action of Pharmacotherapy

Medications approved by the FDA for the management of ADHD include immediate-release and long-acting, extended-release methylphenidate and amphetamine preparations, as well as atomoxetine (Strattera)[91] (Table 3).

Additional information on these drugs can be found in several excellent reviews and reports.[92–95] Methylphenidate and amphetamine compounds, which are stimulant medications, release and/or inhibit reuptake of catecholamines (eg, dopamine and norepinephrine), increasing the level of these neurotransmitters at the synapse,[94] whereas atomoxetine is predominantly a selective norepinephrine reuptake inhibitor.

Efficacy

The efficacy of these compounds has been widely studied and confirmed.[92,95–100] Response rates of >70% have been re-

Table 3. Cardiac Effects of Medications Used to Treat ADHD

			Recommendations for Cardiovascular Monitoring	
Medications	Mechanism of Action	Cardiac Effects and Comments	Class I, Level of Evidence C	Class IIa, Level of Evidence C
Methylphenidate (Ritalin, Ritalin SR, Concerta, Metadate, Methylin, Focalin, Daytrana)	Release and/or inhibit reuptake of catecholamines (eg, D and NE) increase level of these NT at the synapse[94]	Increased HR and BP, no ECG changes[107]	BP, HR	ECG on first visit
Amphetamine (Dextroamphetamine, Dextrostat, Adderall, Vyvanse)	Release and/or inhibit reuptake of catecholamines (eg, D and NE) increase level of NT at the synapse[94]	Increased HR and BP, no ECG changes[107]	BP, HR	ECG on first visit
Atomoxetine (Strattera)	Selective norepinephrine reuptake inhibitor[122]	Increased HR and BP in adults and children, palpitations in adults, no ECG changes[122,154,155]	BP, HR[91,155]	ECG on first visit[91,155]
Clonidine (Catapres)	α_2-Adrenergic agonist	Decreased HR and BP, no ECG changes,[130] rebound hypertension with abrupt discontinuation[133,134]	BP, HR; additional BP when medication is started and weaned	ECG on first visit
Guanfacine (Tenex)	α_2-Adrenergic agonist	Decreased HR and BP, no ECG changes[125,156]	BP, HR	ECG on first visit
Desipramine, imipramine	Block the reuptake of D and NE	Prolongation of QTc, PR, QRS, tachycardia[143]; rare reports of sudden death[46,141]	BP, HR	Baseline ECG and at dose increases PR ≤200 ms QRS ≤120 ms QTc ≤460 ms
Bupropion (Wellbutrin, Zyban)	Decreased firing rate of NE- and S-releasing neurons	Increased BP in adults[136] (not in children[135]) cardiac toxicity with overdose	BP, HR	ECG on first visit[132]

D indicates dopamine; NE, norepinephrine; NT, neurotransmitter; HR, heart rate; BP, blood pressure; and S, serotonin.

ported for both methylphenidate and dextroamphetamine compared with 12% for placebo.[101,102] There are no studies of efficacy in children with congenital or acquired heart disease.

General Side Effects of Stimulant Drugs

The common side effects of stimulant medications include decreased appetite, insomnia, emotional lability, stomachaches, and headaches. These side effects appear to be similar during short-term treatment (≈4 weeks)[101–104] and long-term maintenance.[100,105]

Safety of Stimulant Drugs in Children

Data from multisite clinical trials of both amphetamine- and methylphenidate-based stimulants indicate that these medications are generally safe for healthy children with ADHD.[103–105] Several studies report that nearly 90% of children will experience at least 1 side effect, but the majority are mild (63% to 69%) or moderate (28% to 34%), with 4% reporting severe side effects and with a 15% withdrawal rate from the study.[103,104] Decreased growth rate after long-term stimulant treatment also was highlighted in the naturalistic follow-up of children participating in the Multimodal ADHD study.[106]

General Cardiovascular Side Effects of Stimulant Drugs

On average, there is an increase in heart rate of ≈1 to 2 bpm and an increase in systolic and diastolic blood pressures of 3 to 4 mm Hg.[107] Ambulatory 24-hour blood pressure monitoring has shown similar increases.[108]

In general, these cardiac side effects have been thought to be clinically insignificant for most children with ADHD, but there may be a potential for severe adverse events in some children with certain forms of congenital heart disease or arrhythmias with a predisposition for sudden cardiac arrest.[48] No study has demonstrated a significant change in the QT or QTc intervals,[109] although 1 study showed 1 case of QT prolongation interval >25% with no clinically significant prolongation of the mean QT interval.[110]

Efficacy and Safety of Stimulants in Children With Heart Disease (Structural Cardiac Abnormalities or Other Cardiac Conditions)

There is 1 report of a small open-label study of methylphenidate in 12 children with velocardiofacial syndrome, two thirds with congenital heart disease. This small group of patients showed a significant improvement in this 4-week study, and none had hypertension, tachycardia, or ECG changes.[33] In this small group, these medications in children with heart disease did not cause any harmful effects. On the other hand, there has been a general concern that stimulant drugs have the potential to cause hypertension, tachycardia, or arrhythmias that would be deleterious in children with congenital or acquired heart disease, cardiac arrhythmias, or Marfan syndrome. Additionally, stimulant medications can affect other factors of concern in children with congenital heart disease such as growth, bowel physiology, cardiac arrhythmias, and cardiac function.[95,101–105]

Cardiac Effects of Specific Drugs

Methylphenidates (Concerta, Focalin, Metadate, Methylin, Ritalin)

Methylphenidate has statistically significant but clinically insignificant hemodynamic effects given in therapeutic doses. Reports of sudden deaths directly related to methylphenidate as the sole agent are rare, but there are reports of ventricular arrhythmias and suppression of cardiac function with methylphenidate abuse.[45,111,112]

Amphetamines (Adderall, Dexedrine): Electrophysiological Effects of Amphetamines

Amphetamines have been associated with tachyarrhythmias and sudden death.[113–115] Many of the electrophysiological effects of amphetamines may be initiated by the release of norepinephrine stores from presynaptic vesicles and blocking of norepinephrine reuptake.[116,117] In addition, amphetamines are potent blockers of dopamine uptake and strong central nervous system stimulants.

Dopaminergic Effects of Amphetamines

In addition to the β-agonist effects of amphetamines, the dopamine receptors D1 and D2 contribute to the cardiovascular effects of methamphetamine by producing a pressor response accounting for the increase in blood pressure. The D1 receptor also is involved in mediating the positive tachycardic effects of methamphetamine.[117] Methamphetamine has been shown to increase ventricular wall stress by increasing afterload.[118] This results in an increase in myocardial oxygen demand.

Amphetamine Abuse

The abuse of amphetamines is compounded by the multiple synthetic forms of amphetamine available and the relative ease of production.[119] In addition, the purity of the form of substance taken, route of administration, and abuse of >1 compound (eg, alcohol and methamphetamine) can influence the clinical effects.[120] Myocardial hypertrophy, endocardial thickening, myocardial injury, and cardiomyopathy have been demonstrated in regular abusers of methamphetamine.[115,116,121]

Other Medications Approved for ADHD

Strattera (Atomoxetine)

Short-term studies of atomoxetine found a small but statistically significant increase in mean systolic blood pressure in adults and a marginal increase in diastolic blood pressure in adults and children, which decreased on discontinuation.[122] No ECG changes, including QT prolongation, were noted for all ages. Nonsignificant increases in pulse and blood pressure were found after 1 year of treatment.[122] Mean change in heart rate was higher in poor CYP2D6 metabolizers. Sudden deaths have occurred in children taking atomoxetine, but extensive details are not available.[41]

Other Pharmacological Treatment of ADHD

A medication shown to be effective for which FDA approval for ADHD is being sought is guanfacine (Tenex).[123] Slight decreases in blood pressure and pulse that are not statistically or clinically significant and no ECG changes have been reported for guanfacine.[123,125]

Medications shown to have efficacy and to be used clinically but not FDA approved for ADHD include clonidine[126,127] and bupropion (Wellbutrin).[128,129] Bradycardia and decreased blood pressure have been reported in children treated with clonidine[130] but not in adults[131] or in children with Tourette's disorder.[132] Elevations in systolic and diastolic blood pressure were noted with abrupt withdrawal of clonidine but not with gradual titration.[133,134] ADHD studies in children have shown no significant ECG or vital sign changes with bupropion,[135] whereas significant increases in systolic and diastolic blood pressures have been reported in ADHD adults.[136] No significant cardiovascular effects have been reported in healthy volunteers,[137] although cardiovascular changes have been noted in patients with major depression. In a prospective safety surveillance study of 3100 patients treated with sustained-release bupropion for major depression, 3 patients, each with a preexisting cardiovascular pathology, suffered a myocardial infarction, 2 resulting in death.[138] Tachycardia, hypertension, and increased QTc have been reported in overdoses. The uncorrected QT interval did not differ from that of controls, suggesting that the prolonged QTc probably is not due to cardiac toxicity but may be an overcorrection resulting from the tachycardia.[139]

Effective agents with limited clinical use because of serious adverse effects include the tricyclic antidepressants,[140] limited by reports of sudden death,[1,141] and monoamine-oxidase inhibitors,[142] limited by risk of hypertensive crises. Tricyclics have been reported to cause tachycardia, heart block, orthostatic hypotension, and atrial and ventricular arrhythmias.[143] Several cases of sudden death have been reported in children treated with tricyclic antidepressants. One case of a 6-year-old girl treated with imipramine for social phobia at high doses without ECG monitoring was attributed to possible toxicity.[144] Since 1990, there have been several reported cases of sudden death in children treated with tricyclic antidepressants that were not attributed to overdose and were presumed to be due to cardiac abnormalities.[46,141] At this time, tricyclics are rarely used for the management of ADHD. Although cardiac monitoring is recommended, it is unclear whether monitoring can prevent a catastrophic event. An ongoing large-scale epidemiological study to assess the risk of tricyclic antidepressants may provide more information in the future.

Combination Therapy of Clonidine and Stimulants or Antidepressants

Combining clonidine and stimulants is a common clinical practice frequently used to treat ADHD with comorbid oppositional defiant, conduct disorder, tics, and insomnia.[130,145,146] There are spontaneous reports of sudden death in 4 children treated with the combination of methylphenidate and clonidine in 1995.[147] It has been hypothesized that the cardiovascular effect could have been triggered by the pharmacodynamic interaction between methylphenidate and clonidine, specifically occurring when peak effects of clonidine (sedation-hypotension-bradycardia) coincided with the wearing off of methylphenidate or vice versa (peak methylphenidate effect resulting in activation-hypertension-tachycardia).[127]

Patient Selection for Pharmacotherapy

Medication treatment of ADHD should be limited to individuals meeting diagnostic criteria delineated in the DSM-IV text revision (American Psychiatric Association, 2000). Optimal management of ADHD is achieved with multimodal interventions that can include pharmacotherapy, behavioral therapy, and psychoeducational interventions. Although both stimulant medication and behavioral therapy have been shown to improve symptoms in children with ADHD,[148] the National Institute of Mental Health–funded multisite trial comparing pharmacological and an intensive behavioral treatment for ADHD found that parent and teacher ratings of ADHD symptoms improved significantly more for children on stimulant medication than with an intensive behavioral treatment (MTA Cooperative Group, 1999).

Thus, for most children with ADHD, it has been recommended that stimulant medication should be used as an important component of the treatment plan.[149]

Assessment of Patients for Potential Use of Stimulant Medications

We would agree with the conclusion of a recent special article in *Pediatrics* that states that "there does not seem to be compelling findings of a medication-specific risk necessitating changes in our stimulant treatment of children and adolescents with ADHD."[150] Although those authors suggest that 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," we offer the following recommendations as a refinement of these previous guidelines to aid in the identification of children who are potentially at an increased risk from any type of increased stimulation.

Rationale for Recommendations

The recent FDA press release and requirements for specific heart-related labeling and medication guides leaves the physician with a variety of dilemmas, including the following regarding individuals diagnosed with ADHD in whom stimulant medications would otherwise be prescribed:

- How to know if the child has heart disease or a heart problem or heart defect.
- What to do if the child is known to have heart disease, a heart problem, or a heart defect.
- What to do if the child has heart disease, a heart problem, or a heart defect known to be associated with SCD.

Our intention is to provide the physician with some tools to help identify these children and make determinations about the use of stimulant medications and the follow-up of children on these medications. The goal is to allow treatment of this very significant problem of ADHD while attempting to lower the risk of these products. We acknowledge that the current level of knowledge about these drugs and the specific risks they may impose on children with "heart problems" is limited at this time. However, the benefit of these stimulant drugs in carefully selected individuals has clearly been shown to be highly efficacious.

Screening for Causes of SCD

A combination of careful history, including the patient's medical history, family history, ECG, echocardiograms, and cardiac MRI, may be used to identify the causes of SCD in children, including many of the entities described in the section on SCD in children. The use of ECG and echocardiography as a mass screening tool is controversial and is being debated in terms of both efficacy and cost-effectiveness. European studies have shown the efficacy of an ECG-based screening program in athletes in decreasing the incidence of SCD.[67] Pilot studies are currently underway in the United States to evaluate the efficacy of screening children for SCD.

Recommendations for Assessment

The various stimulant medications carry warnings in their drug monographs suggesting that these medications generally should not be used in children with "serious structural cardiac abnormalities, cardiomyopathy, heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug." Our recommendations stated below are the consensus of the authors and the Council on Cardiovascular Disease in the Young leadership as to the best methods currently available to identify at-risk children before giving them medication and to monitor them safely if stimulant medication is needed to treat their ADHD. They are not intended to limit the appropriate use of stimulants in children with ADHD, to label children with heart disease, or to limit their participation in athletic activities but to add clarity to who has or does not have heart disease and the extent of the risk.

Given the rare association of SCD in those presumed to be predisposed (ie, those with structural cardiac disease as stated in the various drug monographs of stimulant drugs) and in light of the recent FDA advisory panel reports, we recommend the following. After a diagnosis of ADHD has been made but before therapy with a stimulant or other medication is initiated, a thorough evaluation should be performed as indicated below with special attention to symptoms that can indicate a cardiac condition such as palpitations, near syncope, or syncope. All additional medications used, including prescribed and over-the-counter medications, should be determined, and a complete family history should be obtained, especially for conditions known to be associated with SCD, including HCM, LQTS, WPW, and Marfan syndrome. Detection of these symptoms or conditions should warrant an evaluation by a pediatric cardiologist before initiation of therapy. A thorough physical examination for hypertension, cardiac murmurs, physical findings associated with Marfan syndrome, and signs of irregular rhythms should be conducted. Some of the cardiac conditions associated with SCD might not be detected on a routine physical examination. Therefore, it can be useful to add an ECG, which may increase the likelihood of identifying significant cardiac conditions such as HCM, LQTS, and WPW that are known to be associated with sudden cardiac arrest.[48] We recognize that the ECG cannot identify all children with these conditions but will increase the probability.

In 2003, 2.5 million children took medications for ADHD.[151] The number of children who will potentially need to be screened initially will be much greater than those on a continuing or yearly basis.

1. Patient and family history (class I, level of evidence C). The patient history should include questions to elicit the following:

   - History of fainting or dizziness (particularly with exercise).
   - Seizures.
   - Rheumatic fever.
   - Chest pain or shortness of breath with exercise.
   - Unexplained, noticeable change in exercise tolerance.
   - Palpitations, increased heart rate, or extra or skipped heart beats.
   - History of high blood pressure.
   - History of heart murmur other than innocent or functional murmur or history of other heart problems.
   - Intercurrent viral illness with chest pains or palpitations.
   - Current medications (prescribed and over the counter).
   - Health supplements (nonprescribed).

   The family history should include questions to elicit family history of any of the following:

   - Sudden or unexplained death in someone young.
   - SCD or "heart attack" in members <35 years of age.
   - Sudden death during exercise.
   - Cardiac arrhythmias.
   - HCM or other cardiomyopathy, including dilated cardiomyopathy and right ventricular cardiomyopathy (right ventricular dysplasia).
   - LQTS, short-QT syndrome, or Brugada syndrome.
   - WPW or similar abnormal rhythm conditions.
   - Event requiring resuscitation in young members (<35 years of age), including syncope requiring resuscitation.
   - Marfan syndrome.

2. Physical examination (class I, level of evidence C). The physical examination should include an evaluation of the child for the presence of the following:

   - Abnormal heart murmur.
   - Other cardiovascular abnormalities, including hypertension and irregular or rapid heart rhythm.
   - Physical findings suggestive of Marfan syndrome.

3. ECG (class IIa, level of evidence C). A baseline ECG, which often can identify cardiovascular abnormalities (eg, HCM, LQTS, and WPW anomaly), is reasonable to obtain. It is acknowledged that an ECG will not identify all individuals with the cardiac conditions noted above. It can be useful and can increase the sensitivity of the evaluation, especially if there are suspicions of high-risk conditions.

If possible, ECGs should be read by a pediatric cardiologist or a cardiologist or physician with expertise in reading pediatric electrocardiograms.

Once medication is started, if the initial ECG was obtained before the child was 12 years of age, developmental factors associated with puberty may warrant consideration of a repeat ECG. A similar situation is the development of new symptoms or a change in family history after the initial ECG was obtained, in which case a repeat ECG may be useful (class IIa, level of evidence C).

4. Pediatric cardiology consult (class 1, level of evidence C). A consultation from a pediatric cardiologist should be obtained before the stimulant medication is started if there are any significant findings on physical examination, ECG, or history (such as known structural heart

Table 4. ECG Findings

A. Normal or normal variant ECG readings. These ECGs do not require further workup unless clinical symptoms, examination, or history suggest cardiac involvement. The following is a nonexhaustive list of normal or normal variant ECG readings.

1. Sinus bradycardia
2. Sinus arrhythmia
3. Sinus tachycardia
4. Right ventricular conduction delay or incomplete right bundle-branch block without right ventricular hypertrophy or right axis deviation
5. Isolated intraventricular conduction delay
6. Right axis $\leq$8 y of age
7. Early repolarization
8. Nonspecific ST-T–wave changes
9. Juvenile T-wave pattern
10. QTc $\geq$0.45 s by computer but normal by hand calculation
11. Borderline QTc 0.44–0.45 s

B. Abnormal ECG readings that have low likelihood of correlating with cardiac disease. It is possible that a patient with these readings may need to be seen by a cardiologist. The prescribing physician should correlate the ECG reading with the history, examination, and any symptoms the patient might have and discuss the reading with a cardiologist to assess the need for a cardiology office visit. ADHD medication usually does not need to be stopped with these findings. If there is question about stopping medication, we recommend that this be discussed with a cardiologist before stopping. The following is a nonexhaustive list of abnormal ECG readings that have a low likelihood of correlating with cardiac disease.

1. Isolated atrial enlargement, especially right atrial enlargement; this usually will not need further evaluation.
2. Biventricular hypertrophy with only mild midprecordial voltages of 45 or 50 mm; this may need further evaluation.
3. Ectopic atrial rhythms; right atrial, left atrial, wandering atrial pacemaker at normal rates.
    a. Low right atrial rhythms are common, usually are normal variants, and will rarely need further evaluation; other ectopic atrial rhythms are less common and may need further evaluation.
4. First-degree AV block

C. Abnormal ECG readings that may correlate with the presence of cardiac disease. As with B above, the prescribing physician should correlate the ECG reading with the history, examination, and any symptoms the patient might have and discuss the reading with a cardiologist to assess the need for cardiology office visit. It is likely that a patient with this reading will need to be seen by a cardiologist. However, cardiology office visit with examination and further testing/evaluation may not result in diagnosis of cardiac disease. In fact, many of these patients have small likelihood of having significant cardiac pathology that would result in change in the plan of treatment for their ADHD. Therefore, it is not necessary in most cases to immediately stop the medication, but we recommend that this question be discussed with a cardiologist. The following is a nonexhaustive list of abnormal ECG readings that may correlate with the presence of cardiac disease.

1. Left ventricular hypertrophy
2. Right ventricular hypertrophy
3. Wolff-Parkinson-White anomaly or pattern (WPW)
4. Left axis deviation
5. Right axis deviation, especially $>$8 y of age
6. Right atrial enlargement and right axis deviation
7. Right ventricular conduction delay and right axis deviation
8. Second- and third-degree atrioventricular block
9. Right bundle-branch block, left bundle-branch block, intraventricular conduction delay $>$0.12 s in patients $>$12 y of age ($>$0.10 s in patients $<$8 y of age)
10. Prolonged QTc $>$0.46 s
    a. The prescribing physician should ask about medications that might prolong QTc, which could cause mild QTc prolongation, and can be found on Web site http://www.qtdrugs.org
11. Abnormal T waves with inversion V_5, V_6; bizarre T-wave morphology, especially notched or biphasic, or flat and/or ST-segment depression suggesting ischemia or inflammation
12. Atrial, junctional, or ventricular tachyarrhythmias, including frequent premature atrial contractions or premature ventricular contractions

disease, arrhythmias, or a family history of SCD in members <35 years of age).

Table 4 lists significant ECG findings for which a cardiology consult would be recommended.

Recommendations for Administration of Medications and Monitoring

The consensus of the committee is that it is reasonable to obtain ECGs as part of the evaluation of children being considered for stimulant drug therapy. We recognize that there are no clinical trials to inform us on this topic and that there is variance in opinion on this topic. There are no widely accepted recommendations or standards of care for cardiac monitoring on stimulant medications. It is not known if the risk of SCD on stimulants is higher than in the general population or that the approach described will decrease the risk. However, the recent information and warnings regarding cardiac disease warrant reconsideration of the previous approach and thus the recommendations noted in this statement.

Continuing Assessment

Recommendations for Cardiovascular Monitoring of Patients on Specific Drugs

1. Continuing assessment of patients should be made by the pediatrician at each visit by physical examination and by questions regarding potential cardiac symptoms and new family history. Findings should be noted in the history (class I, level of evidence C).
2. Blood pressure and pulse should be evaluated during routine follow-up within 1 to 3 months and at follow-up visits every 6 to 12 months for all medications and more frequently during titration and weaning of the α-agonists (class I, level of evidence C).
3. Any cardiac symptoms should result in appropriate referral and testing to determine whether any serious cardiac side effects are present (class I, level of evidence C).
4. Patient monitoring for specific drugs both before and after stimulant drugs are started is shown in Table 3.

Recommendations for Cardiovascular Monitoring of Patients With Structural Heart Disease or Other Heart Conditions

1. Although concerns have been raised in the drug monographs regarding all individuals with structural heart disease, there are no clinical studies or data indicating that children with most types of congenital heart disease are at significant risk for SCD while on these medications. It is reasonable to consider the use of stimulant medication in patients with congenital heart disease that is not repaired or repaired but without current hemodynamic or arrhythmic concerns or congenital heart disease that is considered to be stable by the patient's pediatric cardiologist unless the patient's pediatric cardiologist has specific concerns (class IIa, level of evidence C).
2. It is reasonable to use stimulants with caution in the following groups of patients (A through G) after other methods of treatment for ADHD have been considered or used (class IIa, level of evidence C).
3. Careful monitoring should be performed after initiation of stimulant medications in the following groups (A through G) (class I, level of evidence C).
   A. Heart condition associated with SCD (LQTS, short-QT syndrome, HCM, arrhythmogenic right ventricular dysplasia, Brugada, coronary anomaly, WPW, Marfan syndrome).
   B. History of an arrhythmia requiring cardiopulmonary resuscitation, direct current cardioversion or defibrillation, or overdrive pacing.
   C. History of an arrhythmia associated with death or SCD.
   D. Previous aborted SCD.
   E. Other clinically significant arrhythmia not treated or controlled.
   F. QTc on ECG >0.46 seconds.
   G. Heart rate or blood pressure >2 SD above means for age.
4. If any of the above conditions or arrhythmias are diagnosed during treatment, consideration should be given to discontinuation of the stimulant medication until further testing and treatment can be achieved (class I, level of evidence C).
5. If arrhythmias are treated and controlled, on approval of a pediatric cardiologist, the patient can be restarted on medication (class I, level of evidence C).

Patients Currently Taking ADHD Medications

For children already taking methylphenidate, amphetamine, or other stimulant agents, it is reasonable to obtain a history, review the physical examination, and order an ECG if these were not previously done as outlined above if deemed necessary (class IIa, level of evidence C).

Evaluation of Risks and Alternatives

Evaluate with the family and other treating physicians as appropriate the risks and alternatives to taking the medication, including the often very significant risks associated with not taking the medication (class I, level of evidence C).

Need for Future Studies

Future studies are necessary to assess the true risk of SCD in association with stimulant drugs in children and adolescents with and without heart disease. A registry, discussed below, would be useful in gathering data on a larger, organized scale. Randomized, double-blind, placebo-controlled studies should be considered. However, the multiplicity of medications used to treat ADHD, the difficulty in the design of such studies considering the complexities of the multiple cardiac diagnoses that exist, the number of patients necessary to provide the statistical power to perform such a study, and the ethics of such a study or studies may make this approach challenging.

Further study is needed to determine the efficacy of universal ECG testing at ≥1 point during childhood to identify children with undiagnosed congenital heart disease and those children with conditions that could lead to sudden cardiac arrest.

Need for an SCD Registry

Considerable interest exists with regard to the establishment of a registry for SCD for children, adolescents, and young adults. The Centers for Disease Control and Prevention attempted an analysis of such data.[152,153] That analysis was driven by *International Classification of Diseases* diagnostic codes and was divided by age group and by inpatient and outpatient setting. Because of the techniques of the analysis, the data were limited, and the incidence of SCD may have been overestimated. To be effective and feasible, an SCD registry should be comprehensive and cross disciplines; it should be extremely detailed for each episode of SCD recorded. For example, useful information from any episode of SCD should include a detailed history of the circumstances of the event, including all medications taken prior to the SCD event, family history, antecedent history, preparticipation screening if it occurred, autopsy results, review by an experienced congenital cardiac pathologist, and postmortem molecular genetic testing of both the index case and first-degree family members if appropriate. Such a registry, even if comprehensively maintained over a short period of time, would allow a more accurate understanding of many questions related to SCD, including the potential association of stimulant drugs and SCD. Other questions such as the true incidence of SCD in children and adolescents and the efficacy of preparticipation screening questionnaires could be answered. In summary, a large-scale, comprehensive registry has the potential to answer many questions that relate to SCD in children, adolescents, and young adults.

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*Modest.

†Significant.

Reviewer Disclosures

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For additional information on ADHD medications and SCD, visit the FDA (www.fda.gov) and American Academy of Child and Adolescent Psychiatry (www.aacap.org) Web sites.

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