

Cardiac risk assessment before the use of stimulant medications in children and youth: A joint position statement by the Canadian Paediatric Society, the Canadian Cardiovascular Society, and the Canadian Academy of Child and Adolescent Psychiatry

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AE Warren, RM Hamilton, SA Bélanger, et al. Cardiac risk assessment before the use of stimulant medications in children and youth: A joint position statement by the Canadian Paediatric Society, the Canadian Cardiovascular Society, and the Canadian Academy of Child and Adolescent Psychiatry. *Can J Cardiol* 2009;25(11):625-630.

Regulatory decisions and scientific statements regarding the management of attention-deficit hyperactivity disorder (ADHD) raise questions about the safety of medications and the appropriate pretreatment evaluation to determine suitability for treatment with medication. This is particularly true in the setting of known structural or functional heart disease. The present paper reviews the available data, including peer-reviewed literature, data from the United States Food and Drug Administration Web site on reported adverse reactions in children using stimulant medication, and Health Canada data on the same problem. A consensus-based guideline on appropriate assessment is provided, based on input from members of the Canadian Paediatric Society, the Canadian Cardiovascular Society and the Canadian Academy of Child and Adolescent Psychiatry, with specific expertise and knowledge in the areas of both ADHD and pediatric cardiology. The present statement advocates a thorough history and physical examination before starting stimulant medications, with an emphasis on the identification of risk factors for sudden death, but does not routinely recommend electrocardiographic screening or cardiac subspecialist consultation unless indicated by history or physical examination findings. A checklist for identifying children who are potentially at risk of sudden death (independent of ADHD or medications used to treat it) is provided. Although recommendations are based on the best evidence currently available, the committee further agrees that more research on this subject is necessary to optimize the approach to this common clinical scenario.

Key Words: Attention-deficit hyperactivity disorder; Consensus statement; Pediatric; Population health; Risk; Sudden death

L'évaluation du risque cardiaque avant l'utilisation de stimulants chez les enfants et les adolescents : Un document de principes conjoint de la Société canadienne de pédiatrie, de la Société canadienne de cardiologie et de l'Académie canadienne de psychiatrie de l'enfant et de l'adolescent

Les décisions en matière de réglementation et les documents scientifiques au sujet de la prise en charge du trouble de déficit de l'attention avec hyperactivité (TDAH) soulèvent des questions quant à l'innocuité des médicaments et à l'évaluation convenable à effectuer avant le traitement afin de déterminer la pertinence d'une pharmacothérapie. Ce constat est particulièrement vrai en présence de cardiopathies structurelles ou fonctionnelles. Le présent article contient l'analyse des données disponibles, y compris les publications révisées par des pairs, des données tirées du site Web de la *Food and Drug Administration* des États-Unis au sujet des réactions indésirables déclarées chez des enfants qui prennent des stimulants, ainsi que des données de Santé Canada sur le même problème. Des lignes directrices consensuelles sur l'évaluation pertinente sont proposées d'après l'apport des membres de la Société canadienne de pédiatrie, de la Société canadienne de cardiologie et de l'Académie canadienne de psychiatrie de l'enfant et de l'adolescent, qui possèdent notamment des compétences et des connaissances précises tant dans le secteur du TDAH que de la cardiologie pédiatrique. Le présent document de principes prône une anamnèse et un examen physique détaillés avant la prescription de stimulants et s'attarde sur le dépistage des facteurs de risque de mort subite, mais il ne contient pas de recommandations systématiques de dépistage électrocardiographique ou de consultations avec un spécialiste en cardiologie, à moins que les antécédents ou que l'examen physique ne le justifient. Le document contient un questionnaire pour repérer les enfants potentiellement vulnérables à une mort subite (quel que soit le type de TDAH ou les médicaments utilisés pour le traiter). Même si les recommandations dépendent des meilleures données probantes disponibles, le comité s'entend pour affirmer que d'autres recherches s'imposent pour optimiser l'approche de ce scénario clinique courant.

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Received for publication September 1, 2009. Accepted September 20, 2009

Pharmacological treatment with stimulant medications has been shown to improve symptoms associated with attention-deficit hyperactivity disorder (ADHD) and is part of the American Academy of Pediatrics treatment recommendations for children with this disorder (1,2). However, recent regulatory decisions regarding ADHD drug licensing and labelling (3,4), along with a recent American Heart Association statement (5), its correction and a response (clarification) by the American Academy of Pediatrics (6,7), have raised questions about ADHD evaluation and therapy among Canadian practitioners. Current Canadian practice in the area of ADHD drug treatment and cardiovascular screening is mixed, with little agreement on the appropriate evaluation of children before starting ADHD medication (8). Opinion is even more divergent regarding the safety of treatment of children with repaired or palliated congenital heart disease (CHD) taking ADHD medications (8).

To provide guidance and clarity for Canadian physicians caring for children with ADHD, the Canadian Cardiovascular Society, the Canadian Paediatric Society and the Canadian Academy of Child and Adolescent Psychiatry developed the present joint position statement. The statement provides consensus-based recommendations on the assessment of cardiac risk in children with ADHD being considered for stimulant treatment. It does not address the diagnosis of ADHD, nor does it consider the therapeutic benefits of stimulant treatment. Similarly, it does not address the relative merits or risks of one medication over another in this patient population. Likewise, nonstimulant medications used in the treatment of ADHD, including atomoxetine, antidepressants and alpha-agonists, are not specifically reviewed.

METHODS

Relevant literature was sought using PubMed searches with MeSH headings of "death, sudden" OR "death, sudden, cardiac" AND "attention deficit disorder with hyperactivity" using the limits "human" and "English" (final search occurred on February 26, 2009). Bibliographies of all retrieved papers were further reviewed for relevant papers that may have been missed in the initial search. Titles and abstracts were reviewed for relevance, and papers that the writing group decided were pertinent were included in the review. The existing consensus statement on this topic from the American Heart Association (5) and its subsequent clarifications (7), including the response from the American Academy of Pediatrics (6), were reviewed, as were bibliographies from these documents. Experts in the field of sudden death (pediatric electrophysiologists) and ADHD (developmental and community pediatricians, and child and adolescent psychiatrists) were consulted through solicited input and opinion. Finally, primary data sources used by regulatory agencies were reviewed. Three authors (Drs AE Warren, SA Bélanger and RM Hamilton) summarized all selected papers and the final document was reviewed, modified and ultimately approved by the members of each organization's writing group. Recommendation grades and levels of evidence are listed in Appendix 1.

BURDEN OF ILLNESS IN CHILDREN AND YOUTH WITH UNTREATED ADHD

In assessing the use of any medication, physicians must weigh the risks of the disease against the risks of the treatment. ADHD is the most common behavioural disorder in children, affecting 3% to 7% of school-age children (1). ADHD affects multiple facets of a patient's life. Many children with ADHD present with school difficulties (9) and have lower self-esteem than non-ADHD children (10). Family stress, psychiatric comorbidities, poor social skills or social isolation, and poor sibling or peer relationships are challenges facing these children and adolescents (11,12).

Adolescents with ADHD are at higher risk for school failure, poor social relationships, motor vehicle collisions, delinquency and

poor vocational outcomes, and are more likely to experiment with tobacco, alcohol, drugs and sex (13). In adolescents, having ADHD may be associated with double the risk for psychoactive substance abuse (14).

In addition, adolescents and young adults with ADHD are more likely than control subjects to be cited for speeding or other traffic violations (15).

ADHD IN CHILDREN WITH HEART DISEASE

Heart disease in children can take many forms, but in North America, structural forms of CHD predominate. Because mortality rates have improved in this group of children, attention has turned to assessing neurodevelopmental outcomes in these patients. Increasingly, the literature shows that children with repaired CHD are at increased risk of also having ADHD (16,17). Shillingford et al (16) found that parents of up to 30% of school-age survivors of cardiac surgery reported clinically significant scores on the ADHD Rating Scale-IV, a standardized instrument for quantification of ADHD symptoms. Hovels-Gurich et al (17) described decreased attention in association with cyanotic heart disease. It is unknown whether observations by both groups are related to surgical or perioperative factors, coexistent genetic conditions or environmental influences. Unfortunately, no studies on the risks and benefits of treating these children with stimulant medications have been published.

Arrhythmic heart disease in children includes rhythm disorders such as long and short QT syndrome, arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome and Wolff-Parkinson-White syndrome. Cardiomyopathies, most commonly hypertrophic or dilated, also occur. All of these conditions are intrinsically associated with varying risks of sudden death, even without stimulant medications. It is unknown whether these children have an increased rate of ADHD in comparison with the general population. The risks of stimulant use in this population are likewise unknown.

SUDDEN DEATH IN CHILDREN AND YOUTH

In contrast to adults, sudden death occurs only rarely in the pediatric population (18,19). Although no estimates of the sudden death rate in Canadian children have been published, rates range from 1.3 to 8.5 per 100,000 patient-years in other countries (18-21). In Italy, the incidence of sudden death in individuals younger than 35 years of age is 0.8 per 100,000 persons per year (22). In a review by Berger et al (23) of multiple series, the median sudden death rates in children was 1.2 to 1.3 per 100,000 patient-years.

Autopsies of young persons with no previously diagnosed heart disease who died suddenly have often revealed heritable cardiac conditions (hypertrophic cardiomyopathy, long QT syndrome, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia or Brugada syndrome) or subclinical structural conditions (coronary artery anomalies) (24). A pre-existing history of cardiac symptoms (syncope, palpitations) or a positive family history of sudden death is often identified in these patients, although frequently misinterpreted (25).

SUDDEN DEATH IN CHILDREN WITH HEART DISEASE

Among young persons with known structural CHD, sudden death is associated with specific conditions, notably tetralogy of Fallot and d-transposition of the great arteries, particularly after the Mustard or Senning procedures (26). The rate of sudden death in children with CHD varies significantly, depending on the nature of the underlying disease (26). Silka et al (26) found an overall sudden death rate of 0.9 per 1000 patient-years (90 per 100,000 patient-years) among patients with selected forms of CHD who had undergone surgical repair. In another study, Nieminen et al

(27) found that 22% of CHD-related late deaths after cardiac surgery were sudden, with 73 of 88 sudden deaths presumed secondary to arrhythmias. Of the 6024 patients who survived their first operation, the overall sudden arrhythmic death rate in this series was 1.2%. In Canada, Sanatani et al (28) found a sudden and unexpected death frequency of 10 patients per year (0.14% of 'patient encounters') over an eight-year period when all postoperative patients followed by a pediatric cardiology service in Ontario were included. Dancea et al (29) found that 36% of structural heart disease was undetected before death in cases of sudden unexpected infant death in Quebec. Only 13% of nonstructural heart disease (such as myocarditis or primary endocardial fibroelastosis) was detected before death.

SUDDEN UNEXPECTED DEATH IN CHILDREN WITH ADHD

In children with ADHD, the risk of death from all causes is estimated to be 58.4 per 100,000 patient-years (30). Regulatory agencies (United States Food and Drug Administration [FDA] and Health Canada) identified 25 sudden deaths in individuals prescribed ADHD medications from Adverse Event Reporting System data, resulting in the current concern over a possible association (6,31,32). However, when the number of patient-years of prescribed medication is incorporated into the evaluation, the frequency of reported sudden deaths per year of ADHD therapy with methylphenidate, atomoxetine or amphetamines among children is 0.2 to 0.5 per 100,000 patient-years (32). While it is recognized that adverse events are frequently under-reported in general, the sudden death of a young individual on medication therapy is likely to be better reported. Thus, using the best available data, it is likely that the risk for sudden death of children on ADHD medications is similar to that of children in the general population. For the reported cases, the frequency of structural heart disease, previous syncope, positive family history of sudden death or conditions potentially associated with sudden death, and association with exercise were similar to that reported for sudden death in the general pediatric population.

A case-control study by Gould et al (33) examined the frequency of stimulant use (as determined from a combination of sources) among those who died suddenly and unexpectedly (SUD group) compared with those who died in motor vehicle collisions. Although it was subject to significant potential recall bias, this study found that the OR for stimulant use in the SUD group was 7.4 (95% CI 1.4 to 74.9). The wide CI reflects the rarity of sudden death in those on stimulant medications, with just 10 cases and two controls among 564 matched pairs reported to be taking methylphenidate. In sensitivity analyses, these findings did not reach statistical significance when parental reports of stimulant use were excluded. An FDA response to this study (34) pointed out other limitations that make these findings difficult to interpret. The limitations include possible reporting biases, other recall biases and the low overall frequency of stimulant use in both groups. As a consequence, the FDA suggested no change in the general approach to ADHD patient care. However, as clinicians, it is important to recognize that exceedingly rare but real risks cannot yet be excluded and should be balanced against the risks associated with failing to treat children with ADHD, and that future research will likely continue to shape our understanding of these risks.

POTENTIAL APPROACHES TO THE PROBLEM

Given the clear need to provide guidance for Canadian physicians caring for children with ADHD and persistent uncertainty regarding this issue within the Canadian medical community, the committee considered a number of potential approaches to this problem. These are outlined below.

History and physical assessment

The use of a structured cardiovascular risk-screening tool in the assessment of children with ADHD has not been tested. However, focused history and physical assessment forms have been recommended to screen for cardiac disease at other times (35). Positive responses on a cardiac functional enquiry, including a history of decreased exercise tolerance in comparison with other children or extreme shortness of breath with exercise; questions specifically about fainting or palpitations with exercise or with startle or fright; and a detailed family history looking for a history of sudden or unexpected death in the family, particularly in individuals younger than 35 years of age (including unexplained motor vehicle accidents, drownings and sudden infant death syndrome cases) are at least theoretically useful in identifying children who are potentially at risk of sudden death, but have not been prospectively evaluated for efficacy. Abnormal findings on cardiovascular examination such as the presence of a pathologic-sounding murmur, or absent or delayed femoral pulses should prompt further evaluation before starting on ADHD medications, as they should for any child. The presence of a known or confirmed functional murmur should not preclude the use of ADHD medications in children who are otherwise well.

In an effort to provide a screening tool that practitioners can use to screen for cardiac disease, the committee proposes the checklist provided in Appendix 2. This table is not intended to be specific for ADHD patients. However, a positive response on any of these items should prompt further investigation or review by a specialist in pediatric cardiology. The absence of any positive response should likewise not be interpreted as a guarantee of 'safety' when using ADHD medications.

Electrocardiogram assessment

There are currently no data on the frequency with which a pre-treatment electrocardiogram (ECG) in the ADHD population would identify an individual at risk for sudden death. ECG screening has been evaluated as a method to prevent sudden cardiac death in athletes in the United States, with an estimated cost of US\$44,000 per year of life saved (36). Japan has performed school-based ECG screening of all children, with an estimated cost of US\$8,800 per year of life saved (37). In Italy, ECG screening of all athletes has been mandated for more than 30 years and is considered to have reduced the incidence of sudden cardiac death in that population by 89% (38). The applicability of the Italian data to other populations has been questioned (39). Frohna (39) pointed to the observational nature of the study, the lack of evaluation of the incremental value of ECG (over history and physical alone) and a higher than usual initial sudden death rate in Italy, among other limitations, as potential reasons to be cautious. Canadian health care jurisdictions do not currently organize or fund ECG screening for athletes or other groups. Consequently, in the absence of any published studies of ECG screening in the ADHD population, there is no current indication to perform an ECG in a child before or during ADHD therapy when history, family history and physical examination are normal and remain so. Moreover, in the absence of high-quality evidence to guide clinicians in the appropriate management of many of the asymptomatic ECG findings that may be discovered, screening in this population may lead to inappropriate discontinuation of helpful treatment and may do more harm than good.

Subspecialty consultation

For the typical ADHD patient with no known heart disease or risk factors for sudden death, the risk of medication is likely to be no higher than that for the general childhood population. Therefore, ADHD medication should be initiated at the recommendation of the person diagnosing and following the patient for the ADHD, and not a cardiologist.

Position statement

For patients with known congenital heart disease or arrhythmias, certain disorders are known to be associated with an increased risk of sudden death. Such patients should already be under the care of a cardiologist. Because there is no compelling evidence that ADHD medications raise the risk of sudden death even further, initiation of ADHD medication should be primarily at the recommendation of an ADHD specialist, although discussion of treatment choices with the responsible cardiologist is appropriate. In some cases, the cardiologist may recommend further investigation before beginning therapy, or specialized surveillance on an ongoing basis. These recommendations should be individualized for the selected therapy and underlying condition.

For patients with newly identified risk factors for coexistent cardiac disease, as per the proposed checklist, consultation with a heart specialist should be sought, regardless of whether ADHD medication will be prescribed. This would also be true in the non-ADHD patient. There is currently no evidence to support routine consultation with a cardiologist before the start of ADHD medication.

CONCLUSIONS AND RECOMMENDATIONS

For each conclusion and recommendation, the level of recommendation and strength of evidence are provided in parentheses following the statement.

- Analysis of patient-year exposure data for children on ADHD medications suggests that the rate of sudden death is similar to the general population. Possible under-reporting, a report of increased odds of stimulant use in patients with sudden death compared with motor vehicle deaths, and rare deaths with the initiation of medication remain reasons for continued research in this area (class IIa, level C).
- CHD patients frequently have ADHD and can potentially benefit from ADHD therapies, including appropriately prescribed medication (class IIa, level C).
- Patients with ADHD, like all pediatric patients, should undergo a careful history and physical examination that includes personal and family history details that may identify those at risk of sudden cardiac death. This should be performed by their primary care physician (class IIa, level C).
- Routine ECG assessment of ADHD patients before starting medication is not supported by evidence and is not recommended (class IIa, level C).
- For ADHD patients without known heart disease, the person managing the ADHD is the appropriate individual to evaluate benefit and risk, and make recommendations for medication therapy (class IIa, level C).

- For ADHD patients with known heart disease who are followed by a cardiologist, the physician with expertise in ADHD likely remains the appropriate individual to evaluate benefit and risk, and make a recommendation for medication therapy, because there is little evidence that taking medication further increases the risk of sudden death. Discussion of treatment options with the cardiologist is appropriate, with ultimate treatment decisions being made by consensus. 'In-person' clinical review by the cardiologist specifically for ADHD risk assessment before starting treatment is generally unnecessary (class IIa, level C).
- For ADHD patients with suspected heart disease or identified risk factors for sudden death, assessment by a cardiologist is recommended. This would also be the case for a non-ADHD patient (class IIa, level C).
- The above points are based on the consensus of a combined group of practitioners from across Canada with expertise in sudden death, general pediatric cardiology, and the care of children and youth with ADHD. Further research is necessary before recommendations satisfying higher levels of evidence criteria can be made (class IIa, level C).

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DISCLAIMER: This article has been jointly prepared by members of the Canadian Cardiovascular Society, the Canadian Paediatric Society, and the Canadian Academy of Child and Adolescent Psychiatry. It is being published simultaneously in the journals of all three societies to facilitate dissemination of the information to the Canadian medical community. Though the content of each article is identical, the author list varies. This reflects the cooperative nature of the statement, and the joint involvement of all of the writing groups and their respective chairs, in the preparation, revision and approval process of the document.

APPENDIX 1

Recommendation grades and levels of evidence

Recommendation grade	Definition
Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment
Class IIa	Weight of evidence in favour
Class IIb	Usefulness/efficacy less well established
Class III	Evidence that the treatment is not useful and in some cases may be harmful
Level of evidence	Definition
Level A	Data derived from multiple randomized clinical trials or meta-analysis
Level B	Data derived from a single randomized clinical trial or large nonrandomized studies
Level C	Consensus of opinion by experts and/or small studies, retrospective studies or registries

APPENDIX 2

Screening tool for the identification of potential cardiac risk factors for sudden death among children starting stimulant medication

Answering "yes" to any of these items should prompt further investigation or review by a specialist in pediatric cardiology

History	Yes	No
Shortness of breath with exercise (more than other children of the same age) in the absence of an alternative explanation (eg, asthma, sedentary lifestyle, obesity)		
Poor exercise tolerance (in comparison with other children) in the absence of an alternative explanation (eg, asthma, sedentary lifestyle, obesity)		
Fainting or seizures with exercise, startle or fright		
Palpitations brought on by exercise		
Family history of sudden or unexplained death including sudden infant death syndrome, unexplained drowning or unexplained motor vehicle accidents (in first- or second-degree relatives)		
Personal or family history (in first- or second-degree relatives) of nonischemic heart disease	Yes	No
Long QT syndrome or other familial arrhythmias		
Wolff-Parkinson-White syndrome		
Cardiomyopathy		
Heart transplant		
Pulmonary hypertension		
Unexplained motor vehicle collisions or drowning		
Implantable defibrillator		
Physical examination	Yes	No
Hypertension		
Organic (not functional) murmur present		
Sternotomy incision		
Other abnormal cardiac findings		

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