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Letter to the Editor

Electrocardiogram before starting stimulant medications: to order or not?

Abstract D is an 8-year-old boy brought to his paediatrician for evaluation. His mother is concerned as his teacher has been frequently complaining that he is very restless and often disturbs the rest of the class by getting up on some pretext or the other. He is unable to concentrate on his work and gets distracted very easily. He makes many careless mistakes and can hardly finish his tasks on time. He is frequently reprimanded for talking during class. He often answers out of turn or before the question has been completed; however, so far, he has been managing to get passing grades. At home, he is constantly on the go while he is awake. If he is forced to sit, like at mealtimes, he fidgets a lot. He also needs to be constantly nagged to do everything, even his daily activities such as brushing his teeth, or he forgets to do them or leaves them incomplete. He takes ages to finish his food. It is a major job to get him to do his homework. His mother says that at home he has been like that since the last 2 to 3 years, but now she is concerned because of the difficulties he is experiencing at school as well. After obtaining his medical history, examination, and getting response from parents and teachers – using Vanderbuilt Assessment Scales – the paediatrician diagnoses him to have attention deficit hyperactivity disorder. Besides behavioural interventions, he considers medications for his management. The paediatrician is debating the merits of performing electrocardiogram and/or referring the boy to a cardiologist before starting stimulant medications. *If you were caring for this patient, how would you proceed?*

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Attention deficit hyperactivity disorder is not uncommon and needs treatment

Attention deficit hyperactivity disorder is the most common neurobehavioural disorder occurring during childhood with a reported prevalence of 5–20% among school-aged children.[1] When untreated, it can lead to significant impairment in the functioning of the child and potentially have a long-term influence on the child's performance, self-esteem, and productivity. Management involves various psychological interventions and medications.

Principles of pharmacotherapy in attention deficit hyperactivity disorder

The basic premise is that a relative deficiency of dopamine is seen in the frontal cortex of children with attention deficit hyperactivity disorder,[2] and this results in an increased background rate of neuronal discharges. By using medications that can increase the dopamine levels, an improvement in higher neurological performance is postulated due to reduction in the frequency of these random neuronal discharges. The medications used to treat attention deficit hyperactivity disorder are broadly classified as stimulants and non-stimulants. The most commonly used stimulants are methylphenidate and amphetamine. The mechanisms underlying the pharmacological effects of the amphetamines are due to direct release of dopamine and norepinephrine from the pre-synaptic neurons.[2] Conversely, the methylphenidate class of action is based primarily on re-uptake inhibition of dopamine and norepinephrine.[2] Atomoxetine works by a similar mechanism, although norepinephrine uptake blockade is the primary mode of effect.[2] The non-stimulant group comprises the guanfacine compounds, marketed as Tenex, and the long-acting version, Intuiv. Their mechanism of action is due to direct stimulation of α1A receptors in the frontal cortex. Guanfacine is structurally and pharmacologically similar to clonidine, and thus may result in mild sedation and an overall decrease in peripheral vascular resistance.

Correspondence to: Dr. Varun Aggarwal, Department of Pediatric Cardiology, Texas Children's Hospital and Baylor College of Medicine, Houston, TX, United States of America. Tel: +1-7863766549; Fax No: (844) 841-4452; E-mail: drvarunaggarwal@gmail.com

Controversy regarding cardiac monitoring

As the term implies, "stimulant" medications can be associated with secondary sympathomimetic effects on the cardiovascular system, resulting in hypertension and tachycardia. These effects have caused considerable debate regarding the need/benefits/risks and cost for a detailed cardiac evaluation before prescribing these stimulant medications.

American Heart Association scientific statement (1999)[3]

The primary concern stemmed from the use of tricyclic antidepressants but no specific cardiovascular monitoring was recommended.

Health Canada (2005)[4]

February 2005: Based on US post-marketing reports of sudden death in children, the sale of Adderall XR in the Canadian market was suspended.
August 2005: Sale of Adderall was re-instated, but with a statement advising healthcare professionals to be aware of the cardiac risk factors before initiating therapy and to avoid stimulant use for all patients with "symptomatic cardiac disease" or "known structural cardiac abnormalities".

Food and Drug Administration advisory panel[5]

February 2006: A warning label was added to Adderall, which stated "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".
February 2006: The Food and Drug Administration advisory panel, by 8-to-7 vote, recommended a "black-box" warning on the risk of sudden death for individuals receiving any stimulant medications.

February 2007: The Food and Drug Administration issued a press release titled "Food and Drug Administration Directs Attention Deficit Hyperactivity Disorder Drug Manufacturers to Notify Patients about Cardiovascular Adverse Events and Psychiatric Adverse Events".

American Heart Association scientific statement (2008)[6]

April 2008: The American Heart Association noted in their statement that a baseline electrocardiogram, which often can identify cardiovascular abnormalities, such as hypertrophic cardiomyopathy, long QT syndrome, and Wolf–Parkinson–White anomaly, is reasonable to obtain. It was acknowledged that an electrocardiogram will not identify all individuals with the cardiac condition noted above. The level of evidence for recommending an electrocardiogram was categorised as class 2A – "weight of evidence/opinion is in favor of usefulness/efficacy" – and assigned it a level of evidence C label – "only consensus opinion of experts, case studies, or standard of care".

American Academy of Pediatrics scientific statement (2008)[7]

May 2008: The American Academy of Pediatrics statement followed the American Heart Association scientific statement. It was recognised that, although the sudden death of a child is a tragedy, there have been no studies or compelling clinical evidence to demonstrate that the likelihood of sudden death is higher in children receiving medications for attention deficit hyperactivity disorder than in the general population. The statement stated that screening electrocardiograms before starting stimulants have an appropriate balance of benefit, risk, and cost-effectiveness for general use in identifying risk factors for sudden death. Until these questions can be answered, a recommendation to obtain a routine electrocardiogram or children receiving stimulant medications is not warranted. Using the American Heart Association criteria, the American Academy of Pediatrics classified this recommendation as 2B – "the level of evidence is less well established by evidence/opinion, additional studies with broad objectives needed". In addition, using the American Academy of Pediatrics classification of recommendations, the American Academy of Pediatrics assigned the recommendation a category D level of evidence – "on the basis of expert opinion without even observational studies". For children with CHD, evaluation by a paediatric cardiologist was recommended.

Canadian Position statement (2009)[8]

Joint statement from the Canadian Pediatric Society, Canadian Cardiovascular Society, and the Canadian Academy of Child and Adolescent Psychiatry stated that routine electrocardiogram before initiation of medications in children with attention deficit hyperactivity disorder was not supported or recommended based on the current evidence available.

Current evidence

Controversies raised by the publications noted above have created much uncertainty among primary caregivers as to how to monitor patients best for whom stimulant medications are being considered. Current evidence does show small increases in mean heart rate (by 1–2 bpm) and blood pressure (by 3–4 mmHg) with the use of stimulant medications such as methylphenidate, amphetamines, and atomoxetine for treatment periods of <2 years.[9] The changes are

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small and have been described as being clinically insignificant.[9] There is no compelling clinical evidence to demonstrate that the likelihood of sudden death is higher in children receiving medications for attention deficit hyperactivity disorder than that in the general population. It has not been shown that screening electrocardiograms before starting stimulants have an appropriate balance of benefit, risk, and cost-effectiveness for general use in identifying risk factors for sudden death.

Before prescribing stimulants

Complete in-depth history should be collected and physical examination should be carried out before initiating stimulant medications for children or adolescents with attention deficit hyperactivity disorder. The patient history should include questions to elicit, but should not limited to the following:

- History of fainting, dizziness, syncopal events, or seizures, especially during or after exercise.
- Previous history of palpitations, increased heart rate, extra or skipped beats, chest pain, or shortness of breath, especially during or after exercise, or any noticeable change in exercise tolerance.
- History of high blood pressure.
- History of heart murmur other than innocent or functional murmur or history of other heart problems such as CHD or rheumatic fever.
- History of chest pains and/or palpitations with inter-current viral illness.
- Current medications, prescribed and over-the-counter, especially supplements and drugs in case of adolescents.

The family history should include the following:

- Sudden or unexplained death at a young age, especially during exercise, or sudden cardiac death or "heart attack" in members before 35 years of age.
- History of cardiac arrhythmias and any family member with a cardiac pacemaker.
- History of any cardiac disease in family members, such as cardiomyopathy, pre-excitation syndromes, long QT syndrome, or abnormal rhythm conditions.
- Any family member requiring cardio-pulmonary resuscitation, especially during young age.

A thorough physical examination should be carried out, especially looking for any abnormal murmur, hypertension, irregular rhythm, or physical stigmata of other diseases such as Marfan syndrome. The aim of the above evaluation was to identify conditions that increase the likelihood of sudden cardiac death, such as hypertrophic cardiomyopathy, long QT interval syndrome, and Wolff–Parkinson–White syndrome.

Opposition to routine electrocardiogram screening before use of stimulants

Thomas et al[10] has reported the results of screening electrocardiograms before stimulant medications in 372 patients; 24 (6.4%) had abnormal findings and 18 were referred for further evaluation, but none of them was found to have cardiac disease. Appropriate stimulant therapy was delayed in six patients because of the electrocardiogram. The mean cost to perform the electrocardiogram screening including the cost of further testing for patients with abnormal results has been described by Mahle et al[11] to be $58 per child. On the other hand, the mean cost to identify a true positive result was $17,163.18. Moreover, it has been reported that ordering the electrocardiogram screen for three common cardiac conditions linked to sudden cardiac death – hypertrophic cardiomyopathy, long QT syndrome, and Wolf–Parkinson–White syndrome – would add less than 2 days to the patient's projected life expectancy.[12]

Case: After performing a thorough history, including family history, and physical examination as described above, the paediatrician could not find any condition that could potentially increase the likelihood of sudden cardiac death in D. Therefore, based on the current evidence, he decided not to obtain an electrocardiogram and started him on amphetamines. The mother was instructed to report immediately if he complains of any chest pain or tachycardia. His progress was monitored and he improved in his performance at both school and home. Follow-up visit at 4 weeks showed no significant increase in heart rate or blood pressure, and the child did not complain of any other problems such as chest pain, palpitations, etc.

Summary of recommendations, based on current evidence

- Stimulant medications do cause a slight increase in heart rate and blood pressure.
- There is no increased incidence of sudden cardiac death with the use of stimulant medications.
- A detailed family history and examination is mandatory before initiation of stimulants.
- Routine electrocardiogram before initiation of stimulant medications has not been shown to add any benefit in preventing sudden cardiac events, and may be associated with unnecessary anxiety in the family and delay in the initiation of treatment.
- All children on stimulant medications for tachycardia, hypertension, chest pain, and palpitations should be monitored. In a child with an underlying undiagnosed arrhythmia substrate, stimulant medications do have a theoretical increased risk of inducing an arrhythmia. Therefore, if a patient on

stimulants experiences palpitations, chest pain, syncope, or any other paroxysmal cardiac event, it should not be taken lightly and should be appropriately evaluated.
- Any known cardiac condition or suspicion of it based on family history or physical examination necessitates evaluation by a paediatric cardiologist and further evaluation.

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Conflicts of Interest

None.

Varun Aggarwal
Department of Pediatric Cardiology Texas Children's Hospital and Baylor College of Medicine, Houston, TX United States of America

Anjali Aggarwal, Danyal Khan
Department of Pediatrics and Pediatric Cardiology Miami Children's Hospital, Miami, Florida United States of America

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