Adderall and cardiovascular risk: A therapeutic dilemma

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Adderall (Shire Pharmaceuticals, Canada) is a preparation of mixed amphetamine salts made up of dextroamphetamine saccharate, dextroamphetamine sulfate, (racemic dextro/levoamphetamine) aspartate monohydrate and (racemic dextro/levoamphetamine) sulfate in equimolar concentrations. Although the use of generic names is normally preferred, the authors elected to use the proprietary name, Adderall, in the present manuscript for brevity.

CASE PRESENTATION

An eight-year-old boy with attention-deficit hyperactivity disorder (ADHD) is seen in clinic. When discussing therapeutic options, his mother raises a concern. Her father died of 'an abnormal heart rhythm', and she has heard that sustained-release ADHD medications are not safe for children with a family history of heart disease.

Are sustained-release amphetamine salts safe to use in children with ADHD?

The issue of the safety of prescribing stimulants is an important and controversial area. The present article aims to outline the controversies surrounding prescription of stimulants, with particular reference to sustained-release amphetamine salts in children with ADHD, and summarize current guidelines to use when prescribing a stimulant.

THE CONCERNS RAISED ABOUT ADDERRALL

Adderall is a preparation of mixed amphetamine salts indicated for the treatment of ADHD.

The extended-release form, Adderall XR, was approved for use in Canada in January 2004. In February 2005, Health Canada suspended Adderall XR's notice of compliance due to 20 global/international case reports of cardiac death and/or stroke in individuals being treated with Adderall that had been submitted to the United States Food and Drug Administration (FDA) adverse event reporting system. Fourteen of these individuals were children (1). In the group included in the FDA adverse event reports, some patients had a toxic level of mixed amphetamines salts, a family history of ventricular arrhythmia, were involved in strenous exercise and were dehydrated. Others had structural cardiac anomalies. Abnormalities described included aberrant origin of coronary arteries, idiopathic hypertrophic subaortic stenosis, bicuspid aortic valve and cardiac hypertrophy. It has been postulated that these anomalies could potentially be adversely affected by stimulant drugs.

In Canada, in 2005, the Adderall XR New Drug Committee, formed under the Food and Drug Act to assess the evidence of these serious adverse effects, concluded that the analyses provided by Shire Pharmaceuticals and Health Canada used different groups of data and were methodologically weak <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ndca_rep_cnma_rap_2005-08-25-eng.pdf>. Furthermore, the Committee stated that there was a theoretical potential for all stimulants to increase the risk of sudden cardiac death and/or stroke. It was not clear whether this risk depended on the stimulant used, or whether the individual participated in strenuous exercise or had underlying cardiac risk factors.

Adderall was, therefore, returned to the Canadian market in August 2005, with recommendations to adjust the labelling to state that all stimulants should be prescribed with caution in patients who are involved in strenuous exercise, use other stimulants or have a family history of sudden cardiac death (1).

On February 9, 2006, the Drug Safety and Risk Management Advisory Committee of the FDA recommended a 'black box' warning describing the cardiovascular risks of stimulants used to treat ADHD (1).

IS THE DRUG EFFECTIVE?

Multiple trials (2,3) have shown Adderall to be an effective treatment for ADHD compared with placebo, with the added benefit of once daily dosing. In addition, it is as effective or more effective when compared with other stimulants and nonstimulants used in ADHD treatment (3-6).

There are inconsistent findings to whether the side effects of Adderall are dose related. The overall incidence of adverse effects is low and comparable with other stimulants (4). The most commonly reported adverse cardiovascular effects are elevated blood pressure and heart rate, seen in both short-and long-term treatment trials. This rise is generally thought to be statistically but not clinically significant (7). It has been suggested that there is the potential risk that chronically and consistently elevated blood pressure and heart rate could contribute to later cardiovascular morbidity. Thus, it may be

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prudent to undertake ongoing blood pressure and heart rate monitoring for children who are on stimulants (8,9).

It is still not known whether the risk of sudden cardiac death in children who are on stimulants is higher than in the general population because adverse event reporting in Canada and the United States is dependent on voluntary reporting by health practitioners. The lack of a formal monitoring system makes the estimate of such death rates problematic at best (10). In adult studies (2) specifically looking at the cardiovascular effects of Adderall, it was found to be safe in patients with essential hypertension. In otherwise healthy adults, 3% (n=223) of patients experienced cardiovascular side effects including hypertension, palpitation or tachycardia; this adverse event rate is consistent with the anticipated adverse event rate of 5% associated with most cardiovascular drugs (2). The incidence of cardiac anomalies in children with ADHD is believed to approximate that of the general population and, thus, there is no a priori reason to suspect that children with ADHD are a special-risk population, with respect to having a higher rate of anomalies potentially impacted by stimulant therapy.

SUGGESTED PLAN FOR PRESCRIBING ADDERALL

Given the significant morbidity associated with untreated ADHD (11), the proven benefits and potential side effects of Adderall, the following are recommendations for the workup and monitoring of children needing treatment with Adderall. These measures are in addition to current general recommendations for the prescription of stimulant medications in children and are intended for use by community-based and primary child health care providers.

PRETREATMENT CONSIDERATIONS

Treatment should only be considered once a diagnosis of ADHD is confirmed using the *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition* or the *International Classification of Diseases – Tenth Edition*. Only patients with moderate to severe impairment in two different settings should be started on treatment.

WORKUP BEFORE STARTING ADDERALL (RECOMMENDATIONS FROM THE AMERICAN HEART ASSOCIATION STATEMENT [12])

Important points in the past medical history

- History of fainting or dizziness, particularly with exercise;
- Chest pain or shortness of breath with exercise or noticeable unexplained change in exercise tolerance;
- Seizures;
- Rheumatic fever;
- Palpitations, fast heart rate or skipped heart beats;
- History of heart murmur other than innocent (functional) murmur, or history of other heart problems;
- Intercurrent viral illness associated with chest pain or palpitations;
- History of hypertension;
- Medications (prescribed, over-the-counter and alternative); and
- Health supplements (nonprescribed)

Important points in family history

- Sudden or unexplained death in someone young;
- Sudden cardiac death or 'heart attack' in members younger than 35 years of age;
- Sudden death during exercise;
- Cardiac arrhythmias;
- Hypertrophic cardiomyopathy or other cardiomyopathy, including dilated cardiomyopathy and right ventricular cardiomyopathy (right ventricular dysplasia);
- Long QT syndrome, short QT syndrome or Brugada syndrome;
- Wolff-Parkinson-White syndrome or similar abnormal rhythm conditions;
- Event requiring resuscitation in young members (younger than 35 years of age), including syncope requiring resuscitation; and
- Marfan's syndrome.

Physical examination

- Presence of a pathological murmur;
- Irregular heart rate;
- Tachycardia;
- Hypertension; and
- Physical findings suggestive of Marfan's syndrome.

Baseline investigations

A supplementary statement (13) released in August 2008 by the American Academy of Pediatrics did not recommend getting an electrocardiogram (ECG) to screen for heart problems before prescribing stimulants. However, if the patient has suspected cardiac disease including suspected arrhythmia and/or syncope, an ECG should be obtained. The ECG should be read by a paediatric cardiologist, a cardiologist with experience in paediatric ECGs or any physician with experience in reading paediatric ECGs. If the initial assessment described above reveals any features raising concerns of cardiovascular disease in the child or family members, a referral for assessment with the cardiologist should be made before prescribing a stimulant.

MONITORING DURING TREATMENT

- Perform a cardiovascular examination on each visit. Record baseline heart rate and blood pressure before starting Adderall. Obtain repeat readings during follow-up visits (at a minimum annually). Consider reducing the dose or stopping medication if three consecutive readings on separate days are above the 95th percentile for age; alternately, consultation with a physician expert in the evaluation of children with hypertension and provision for assessments, such as 24 h blood pressure monitoring, may be considered.

- Ask about cardiovascular and other side effect symptoms at follow-up visits, for example shortness of breath, chest pain, palpitations, syncope, dizziness, insomnia, headaches, social withdrawal, tics and weight loss.
- Ask if there is any new family history.

Going back to our case, it would be important to get an accurate history of the father's death; particularly his age at the time, and whether this was an unexpected death, what diagnosis was made with respect to the heart arrhythmia, if any, and whether there were any other family members with heart disease.

This patient may then require a full cardiovascular assessment. This would include a baseline ECG if an arrhythmia was suspected (eg, if this was a sudden unexplained death in view of the potential for inherited arrhythmia). In the event that there was a cardiac concern arising from this assessment, the use of stimulants would have to be considered with caution, pending a cardiology referral.

The evidence was gathered from a MedLine search in OVID (1966 to 2007) using the following terms: Adderall, Adderall XR, ADHD, children, treatment, stimulants, sudden death and side effects.

Guidelines for stimulant use were reviewed from the following organization/association Web sites: the Canadian Paediatric Society, the American Academy of Pediatrics, the Royal College of Paediatrics and Child Health, and the American Academy of Child & Adolescent Psychiatry.

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