

APPENDIX 8

POTENTIAL CARDIAC RISKS OF ADHD MEDICATIONS:

Regulatory and Clinical Background, and Practical Recommendations

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Regulatory History

In May, 2006, Health Canada issued important safety information on ADHD medications which included the following warning:

- ADHD drugs should be started at the lowest possible dose, and increased slowly, as individual patient response to these drugs is known to vary widely.
- ADHD drugs should not be used if a patient has: symptomatic cardiac disease; moderate to severe hypertension; advanced arteriosclerosis; or hyperthyroidism.
- ADHD drugs should generally not be used in patients with known structural cardiac abnormalities.
- Before prescribing an ADHD drug, it is important to be aware of whether the patient: has a family history of sudden death or death related to cardiac problems; participates in strenuous exercise; or takes other sympathomimetic drugs; as these are thought to be additional risk factors. In patients with relevant risk factors, and based on the physician's judgement, further evaluation of the cardiovascular system may be considered before starting on the drug.
- Patients who are considered to need long-term treatment with ADHD drugs should undergo periodic evaluation of their cardiovascular status, based on the physician's judgement.
- Patients taking drugs for the management of ADHD are being advised not to discontinue their medication without consultation with their physician.
- Similar information will appear in the Information for the Patient materials for these drugs.

The complete article is available on the www.caddra.ca website and should be read by any clinician who is contemplating treatment in a patient they deem as being at risk. The CAP-G Committee enlisted the help of two prominent Canadian cardiology consultants to prepare some guidance in at-risk patients who have a combination of some prior history of cardiac problems and ADHD. The opinions are those of the consultants and were not peer-reviewed, but were written to provide guidance to physicians who need direction in complicated cases.

Clinical Recommendations

American Heart Association Recommendations for Monitoring

In the American Heart Association Scientific Statement: Cardiovascular Monitoring of Children and Adolescents Receiving Psychotropic Drugs (A Statement for Healthcare Professionals) [84, 85], the Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young states that:

1. "Reports of sudden deaths of children and adolescents treated with psychotropic medications have raised concerns regarding the appropriateness of this therapy, as well as the advisability of baseline and periodic electrocardiographic (ECG) monitoring of such patients."
2. "Stimulants such as the amphetamines and methylphenidate (Ritalin®) cause slight but clinically insignificant increases in heart rate and blood pressure."
3. "Clonidine, a widely used antihypertensive medication, has been associated with two deaths in patients who also received methylphenidate, but the mechanism for these deaths is unknown and may have been sudden cessation of treatment."

The American Heart Association Recommends:

1. Before therapy with psychotherapeutic agents is initiated, a careful history should be obtained with special attention to symptoms such as palpitations, syncope, or near syncope. Medication use (prescribed and over-the-counter) should be determined. The family history should be reviewed with reference to the long QT syndrome or other causes of sudden, unexplained death. Detection of these symptoms or risk factors warrants a cardiovascular evaluation by a pediatric cardiologist before initiation of therapy.

2. At follow-up visits, patients receiving psychotropic drug therapy should be questioned about the addition of any drugs and the occurrence of any of the above symptoms. The physical examination should include determination of heart rate and blood pressure.

Conclusions

Sudden death in the young is fortunately very rare (1.2 - 1.3/100,000 population)

Sudden death in the ADHD population occurs in similar proportion to the general population, even if only 50% of cases have been reported. However, higher rates of under-reporting could be concealing an ADHD effect on sudden death, and rare deaths have occurred on the first day of administration.

Associated conditions in patients with sudden death on ADHD medications are very similar to those with sudden death in the general population (structural heart disease, history of syncope, family history of sudden death, exercise triggering sudden death), and some of these clues can help to suspect a higher risk sudden death, whether in the untreated or treated population.

ECG abnormalities can identify some individuals in the general population at risk for sudden death, and has been recommended and implemented as a cost-effective screening tool in some at risk populations, such as competitive athletes. Cost-efficacy in the general school-age population is less clear and the usefulness of ECG screening in patients being treated with or considered for ADHD medications is unknown. There is no consensus here, and American Heart Association recommendations for ECG screening relate specifically to tricyclic antidepressant therapy or phenothiazine therapy rather than for stimulant medications used to treat ADHD.

The small (but unproven) potential contribution of ADHD drugs to the rare incidence of sudden death in children and adolescents must be weighed against the clinical benefit of the medication. Risk/benefit should be discussed with the parent/patient as appropriate.

In patients with cardiac conditions that place them at increased risk for sudden death, ADHD medications should be contemplated only after cardiologic consultation and a thorough discussion of the risks and potential benefits with the patient, family and consultants.

Questions that are often posed include the management of patients with combined cardiovascular risk and concurrent ADHD.

Q: Is there a way to specifically know ahead of time the risk of sudden death in individual patients with ADHD, and the potential increase in risk in such patients following treatment?

A: It is not possible to accurately assess the magnitude of increases in risk with ADHD medications, or even if there is any increase in risk. However it is helpful to consider, for discussion purposes, some possible numbers to place these risks in perspective. If the risk of sudden death in an individual without evident structural heart disease is approximately 1 per 100 000 /year (age under 25), then even a 50% increase in risk would translate into an absolute increase of 0.5/100 000 deaths/year, or a 1/200 000 chance of death.

Q: Are there disorders where structural cardiac defects pose low risk?

A: Patients with cardiac conditions whose sudden death risk is only marginally elevated from the general population are likely at very low risk if taking ADHD medications. Risks/benefits should be discussed with the parent/patient as appropriate. Such conditions might include (but not be limited to):

- Patients with an asymptomatic or well-repaired atrial septal defect
- Patients with a small or well-repaired ventricular septal defect
- Patients with a well-repaired coarctation of the aorta, without hypertension or significant associated aortic valve disease
- Patients with a mild or well-repaired pulmonary valve stenosis

Q: What reasonable steps should be taken to ensure patients' cardiovascular safety before starting pharmacological

therapy for ADHD?

A: As described above, patients and families should be questioned about a family history of sudden death, a history of loss of consciousness particularly with exercise, and a history of marked exercise intolerance. There is no proof that routine 12 lead ECGs are useful in screening in unselected patients, and most consultants do not recommend such screening unless there is a history or symptoms to suggest cardiac disease. During follow up, new onset syncope, severe dizziness, or exercise intolerance should be asked about, particularly in the early months of pharmacological treatment. If any of these symptoms occur, these should prompt a referral to a pediatrician or a cardiologist, and a consideration at least temporarily stopping the medication for ADHD.

If an ADHD pharmacological treatment is contemplated in a patient with previously known structural heart disease, or in a patient who has a personal or a family history of syncope or sudden death respectively, a pediatric or cardiologic consultation prior to ADHD pharmacological treatment is strongly advised.

It must be emphasized that in the average child or adolescent with ADHD, who has no cardiac symptoms, the risk of cardiac adverse events from ADHD medications is extremely low. On the other hand, a cautious and vigilant attitude with respect to the potential risks is highly advisable.