

# 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 drugs which included the “black box 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.**

A black box warning is a type of warning that appears on [prescription drugs](#) that may cause serious [adverse effects](#). (It is so named for the black border that usually surrounds the text of the warning) A black box warning usually means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening [adverse effects](#).

Health Canada had previously suspended the ADHD medication: Adderal XR (extended release mixed amphetamine salts) on Feb. 9, 2005. Health Canada applied the precautionary principle in the case of the Adderall XR suspension. [1] The precautionary principle is a [moral](#) and [political](#) principle which states that if an action or policy might cause severe or [irreversible](#) harm to the public, in the absence of a [scientific consensus](#) that harm would not ensue, the burden of proof falls on those who would advocate taking the action. It implies a willingness to take action in advance of scientific proof or

evidence of the need for the proposed action on the grounds that further delay will prove ultimately most costly to society. It is usually most stringently applied by stating that proponents of a new potentially harmful technology must show the new technology is without major harm before the new technology is used. A “New Drug Committee” was formed, and heard evidence from expert witnesses representing both Health Canada and the manufacturer of Adderall XR. Following revision of the Adderall XR Product Monograph, the suspension of Adderall XR was ended on August 26, 2005.

In February 2006 the FDA’s Drug Safety and Risk Management Advisory Committee voted 8-7, with one abstention, in favor of a "black box" warning for ADHD drugs after hearing about the deaths of 25 people, including 19 children, who had taken the drugs.. In March 2006, the FDA’s Paediatric Advisory Committee voted by a 15-0 consensus to reject recommending that ADHD drugs bear a “black box” warning of potential cardiovascular and psychiatric risks.

Health Canada provides a rationale for their black box warning in a section entitled: “**Cardiovascular Adverse Events Associated with ADHD Drugs**”:

*“Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. All medications for the treatment of ADHD are sympathomimetic. The stimulatory effects from these drugs on the sympathetic nervous system are usually mild or moderate, but in patients of all ages, particularly those with cardiovascular compromise, these effects may result in serious adverse events including sudden/cardiac death. Reports of these serious adverse events are very rare.”*

*“In patients treated with ADHD drugs, neither clinical studies nor post-marketing reports have shown to date that the incidence or reporting rates of serious cardiac adverse events, including fatalities, are greater than background rates. Additionally, there is no evidence to show that, in terms of cardiac risk, any one of the drugs indicated for the management of ADHD is better or worse than the others. There is ongoing international discussion about the best way to design clinical studies to further investigate these issues.”*

### **Surveillance Data**

Health Canada’s decision to withdraw the Adderall XR was based on very rare, U.S. spontaneous reports of sudden deaths, in pediatric and adult patients, with ADDERALL and ADDERALL XR.

There were 20 reported deaths, including 2 reports which appeared to be the same individual. The death reports occurred predominantly in children (14/20) and young adults (only 2 were > 35 yrs.). Based on IMS prescription data, the Estimated Reporting Rate for Adderal IR/XR was 0.55/100,000 patient-years. Assuming 50% under-reporting, this death rate approximates the expected sudden death rate for young individuals (<35 yrs.) in the general population (1.2/100,000/yr.)

Of the 20 Adderal IR/XR reports, 11 (55%) had associated cardiac risk factors, 6 (30%) were associated with exercise and 6 (30%) were associated with concomitant drugs that may potentially increase the risk of sudden death. Only 2 (10%) had no known associated factor. The profile of sudden death cases on Adderall IR/XR is consistent with age-matched general population, where 40% of cases have structural or familial cardiovascular risk factors and 30% of cases occur while exercising.

When confidence intervals are considered, there is insufficient evidence to support the belief that there is an increased risk of SCD for Adderall compared to other ADHD drugs (DHPL Aug 2005) However, of note: 2 deaths occurred within 1 day of starting Adderal (one in a child with undiagnosed hypertrophic cardiomyopathy, and one in the child of a mother with known ventricular tachycardia).

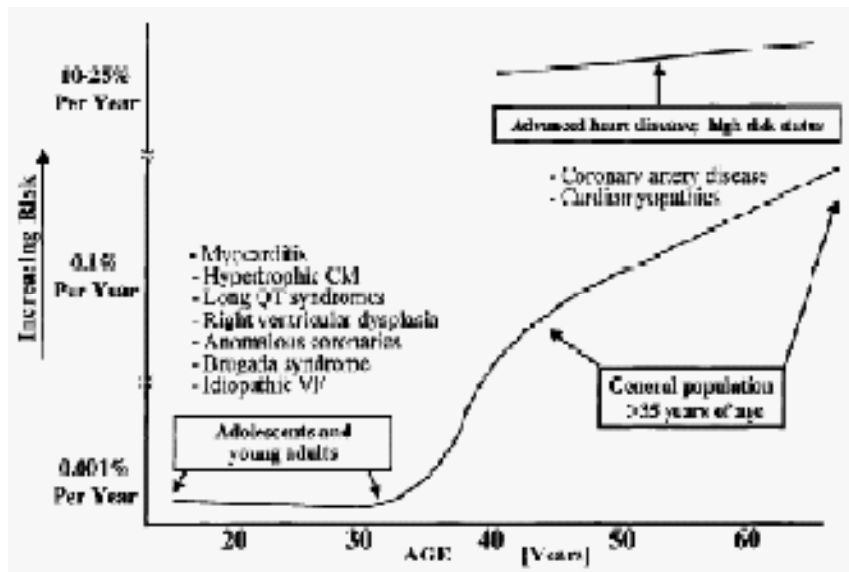
The FDA reports 25 deaths between 1999 and 2003 in patients taking ADHD medications, nineteen involving children. Seven fatalities were associated with either Ritalin or Concerta (methylphenidates). These regulatory actions and observations do not resolve the difficult question of the potential for ADHD medications to increase the risk of sudden death or the magnitude of this risk if it exists. We will place these potential risks in clinical perspective below, and make recommendations for mitigating these potential risks.

### **The Epidemiology of Sudden Death in the Young**

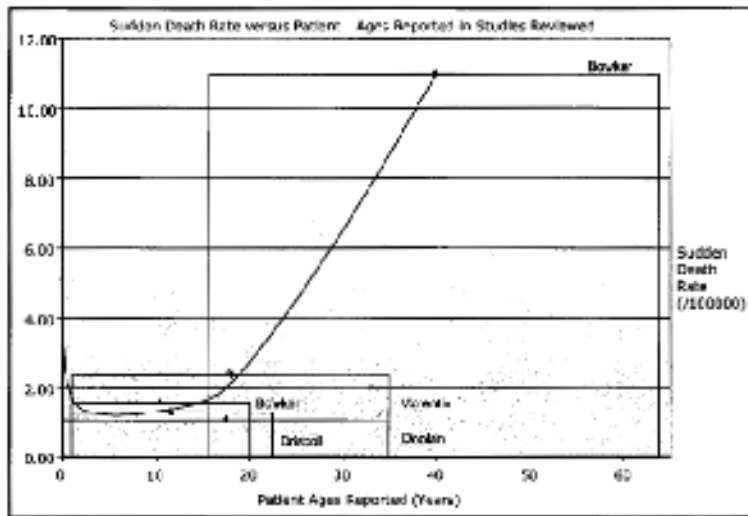
Sudden death is usually of cardiac origin, and is defined as sudden, unexplained, instantaneous death.

Sudden death is most often due to ventricular fibrillation or ventricular tachycardia.

Around age 40 and beyond, coronary artery disease is the most common substrate leading to ventricular fibrillation or ventricular tachycardia, resulting in a much higher risk of sudden death than in adolescents and young adults. (Figure 1, Myerburg et al)



**Figure 1:** (from Myerburg and colleagues) [2] Myerburg estimates the risk of sudden cardiac death is 0.001% per year (1/100,000 per year) with disorders such as myocarditis, hypertrophic cardiomyopathy, long QT syndrome, right ventricular dysplasia, coronary anomalies, Brugada syndrome and idiopathic VF being the commonest causes.



**Figure 2:** Plot of midpoint and range of four epidemiologic studies of the incidence of sudden death in children and young adults. Incidence is 1.2 to 1.3/100,000 per year in children and adolescent. [3-6]

Younger individuals are much less likely to have the coronary artery disease substrate for ventricular fibrillation or ventricular tachycardia. In young patients, structural heart disease such as congenital heart disease is usually clinically evident and leads to diagnosis and ongoing care by a cardiologist. However, some forms of structural heart disease, such as *hypertrophic obstructive cardiomyopathy* and *right ventricular dysplasia* may not be easily diagnosed. Other structural heart disease, such as an anomalous origin of a coronary artery, may not be apparent or diagnosed. However, some patients may be at risk of sudden death even though their heart is structurally normal.

***Non-structural heart diseases*** or “channelopathies” are a diverse group of heritable disorders of ion channel function that can cause ventricular arrhythmias.

**Channelopathies are an** increasingly recognized as an important cause of sudden death in young people with no structural heart problems. The echocardiogram and physical exam are normal, but the ECG is frequently abnormal. (e.g. the QT interval is long, certain kinds of ST elevation, etc.)

Sudden cardiac deaths in adolescents and young adults are fortunately rare. [3-6] The age ranges and midpoint death rates are shown in figure 2. The sudden death rate among adolescents is approximately 1.2 to 1.3 per 100,000 population. Within studies of young patients with sudden death, predisposing factors included hypertrophic cardiomyopathy or left ventricular hypertrophy in 15-22%, and myocarditis in 12-22%. No risk factor could be identified in 18-42% A prodrome of dizziness occurred in 16%, and chest pain in 25%. Syncope prior to the terminal event is common.

Although regular physical exercise including strenuous exercise has undoubted cardiovascular (and other) health benefits, strenuous, particularly anaerobic, exercise may rarely precipitate life threatening arrhythmias in pre disposed patients. A substantial minority of the patients in whom sudden death occurred while taking ADHD drugs where in engaged in vigorous exercise, but this association is equally frequently seen in young victims of sudden death who are not taking any drug therapy. In the absence of structural heart disease, or rare conditions in which exercise habitually causes arrhythmias, the risk of developing serious arrhythmias or sudden death during exercise, in patients receiving drugs for ADHD, is extremely low.

Although the actual number of deaths from unusual cardiac conditions in adolescents is small, the prevalence of the predisposing conditions is higher. The prevalence of Hypertrophic Cardiomyopathy is between 1/500 and 1/1000. The prevalence of Long QT Syndrome is between 1/3000 and 1/5000. The prevalence of Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy is at least 1/5000. [7]

Triggers for sudden death vary depending on the disorder, such as loud noises or physical/psychological stress (long QT syndrome); exercise (“catecholaminergic VT”), drugs which prolong the QT interval (long QT syndrome); fever or during sleep (Brugada syndrome).

Increased levels of circulating or neuronally released catecholamines (“adrenergic stress”) can trigger VT or VF in predisposed individuals – the probability of such triggering is normally very small, but many VT/VF episodes are so triggered. Typical situations are exercise, especially vigorous or anaerobic, extreme stress and anger.

### **Clues to the potential risk of sudden cardiac death**

A cardiologist will have already identified most patients with congenital heart disease by late childhood and adolescence. Among the remaining unidentified patients, clues that heart disease is present include:

- Severe exercise intolerance
- syncope , especially during exertion
- Family history of sudden death esp. at an early age
- syncope with physical or emotional stress

## **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), [8, 9] 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 2 deaths in patients who also received methylphenidate, but the mechanism for these deaths is unknown and may have been sudden cessation of treatment.”

They recommend:

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.

Electrocardiographic 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 stimulant medications used to treat ADHD.

The small potential (but unproven) 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 medication should be contemplated only after cardiologic consultation and a thorough discussion of the risks and potential benefits with the patient, family and consultants.

*Questions regarding the management of patients, who may benefit from drugs for ADHD, with respect to cardiovascular risk, are often posed. We detail with some of these possible questions and answers below.*

**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 drugs, 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 poses 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. Risk/benefit 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 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 drug treatment. If any of these symptoms occur, these should prompt a referral to a pediatrician or a cardiologist, and considering at least temporarily stopping the drug for ADHD.

If an ADHD drug 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 drug 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 drugs is extremely low. On the other hand, a cautious and vigilant attitude with respect to the potential risks is highly advisable.

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