Rethinking the Safety of Stimulants in ADHD
With a black box warning likely to be introduced, should we alter our approach to treatment? Here’s an update on cardiovascular risks associated with stimulant use.

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Neurologists and others who prescribe stimulants for ADHD patients are facing increasing public concern about possible cardiovascular risks. In February 2006 the Drug Safety and Risk Management advisory panel of the Food and Drug Administration met and reviewed reports of sudden death and cardiovascular events including stroke, cardiac arrest and palpitations. They reviewed reports of 25 sudden deaths (19 of whom were children under the age of 18 years) and 43 cardiovascular events (26 children) during the five years between 1999 and 2003. Overall, the risk of sudden death was approximately one in a million exposures, but it was suggested that the increased risk was sufficient to recommend more stringent warnings than have been in place over the 50 or more years that this class of drugs has been in common practice.

That panel voted eight to seven to add a “black box” warning to all stimulants. On March 22 the pediatric advisory committee rejected the most severe “black box” warning. However, they concurred with the earlier advisory committee and recommended adding more information to the labels for the benefit of doctors, patients and families.

Recommendations at the committee level are still open to the discretion of officials at the FDA. Still, Dr. David Graham, a medical officer at the FDA’s Center for Drug Evaluation and Research announced to reporters: “There’s smoke. Does that mean there’s fire? … We wouldn’t be going through this exercise if we didn’t think there was a real possibility of increased risk.” What is the basis of the concern, what is the neurologist to do, and how can we help our patients receive safe and effective treatment?
Safety of Stimulants in ADHD

Origins of the Concern
Likely, the public outcry started with the suspension of marketing of Adderall XR in February 2005 by Health Canada (the Canadian version of the FDA). The situation did not quiet down when Adderall XR was subsequently reintroduced to the Canadian market. And now the FDA has weighed in, although no decision has yet been rendered at the time of this report.

In fairness to those who blame Health Canada for inciting public hysteria by sensationalizing US data previously known to the FDA, there has always been concern that drugs which act as stimulants — with sympathomimetic effects that increase blood pressure and pulse rate — might have potential risks to cardiovascular health. Indeed, the American Heart Association’s Committee on Congenital Cardiac Defects of the Council on Cardiovascular Disease in the Young published a report in 1999. While they did not exonerate methylphenidate or pemoline (the only stimulants with sufficient general experience at the time), they concluded that “no specific cardiovascular monitoring was felt to be indicated” for these medications. To date, there are still no widely accepted recommendations or standards of care for cardiac monitoring when an individual is taking amphetamine (e.g., Adderall, Dexedrine) or methylphenidate (e.g., Ritalin, Concerta, Metadate, Focalin) compounds.

There are several recent reports that specifically address cardiovascular effects of the most popular long-acting preparations of the two primary stimulants. Both immediate as well as chronic cardiovascular effects of Adderall XR were analyzed from two of the pivotal studies including the two-year open label extension of a large four-week randomized double blind, placebo controlled study as well as a much smaller six-week randomized double blind cross-over analog classroom trial. Overall, almost 570 children were involved in the short-term studies or open label extension over two years. During the two short-term trials, there were no significant adverse cardiovascular side effects. There was no statistical impact of Adderall XR on pulse or blood pressure at any of the doses studied (10, 20 and 30mg daily). No subject had to discontinue treatment or lower their dose due to adverse cardiovascular issues.

In the open label extension trial, all individuals started with an initial dose of 10mg of Adderall XR (independent of dose in the double blind phase) with weekly adjustments up to a maximum of 30mg regardless of body weight. Blood pressure and pulse were measured at baseline, weekly for the first month and monthly through the two-year duration. EKG was performed at baseline and again at 12, 18 and 24 months. Results from the long term study showed no evidence of serious cardiovascular problems. Mean blood pressure and pulse changes were minimal and clinically insignificant. No child had to drop out due to cardiovascular problems. Of course, group data can hide individual variation, but the few individual clinically important elevations in blood pressure or pulse were all transient and resolved without intervention while Adderall XR was continued. There were occasional EKG findings of sinus arrhythmia, ST-T wave abnormalities and poor anterior R wave progression; all were considered clinically insignificant by a pediatric cardiologist.

Out of 568 individuals in the long-term study, there were four who dropped out from adverse cardiovascular effects. These included one with moderate tachycardia felt to be directly related to the drug; two with mild, intermittent chest pain possibly related to the stimulant, and one with moderate hypertension also felt to be possibly related. The authors concluded that the risk of Adderall XR was minimal in healthy children who were exposed to clinically insignificant elevations in blood pressure and pulse.

A similar analysis was carried out by the same group which analyzed the one-year open label extension data from several different Concerta studies. Subjects started the open label phase at the initially assigned dose (12, 36 or 54mg daily). Pulse and blood pressure were monitored at monthly visits. There were small but significant increases in both pulse and blood pressure associated with Concerta. Mean pulse elevation was 3.9 beats per minute, systolic blood pressure increased by a mean of 3.3mm Hg and diastolic blood pressure went up by 1.5mg. All findings were significant at P value of 0.001. The question remains whether statistical significance equates to clinical significance. Interestingly, there was no evidence of any tolerance to these effects since there were no differences in pulse or blood pressure between the values at one month and those at 12 months. The authors concluded that there was a statistically significant but clinically insignificant effect of Concerta on blood pressure and pulse.

Likelihood of Adverse Events
Of course, it may be difficult to translate findings to clinical practice from well controlled investigational trials where subjects are carefully screened, frequently monitored for adverse effects, and concomitant drugs tightly regulated. A child with a history of a heart condition would never get enrolled, and he or she would not be allowed to take other medications that might expose the child to increased cardiovascular risk. True, the package insert for Adderall XR includes warnings against using the drug in patients with structural cardiac abnormalities, symptomatic cardiovascular disease, moderate to severe hypertension, advanced atherosclerosis and hyperthyroidism. Concerta recommends caution in treating patients whose underlying medical condition could be compromised by increases in blood pressure or pulse (e.g., pre-existing hypertension, heart failure, recent myocardial infarction or hyperthyroidism). Focalin XR has the same class warning. But while ADHD is a common disorder, cardiovascular disease in children is uncommon, and many clinicians caring for children have weighed the disability of the attentional disorder against the apparently low risk of cardiovascular side effects.
A review of the specifics of the cases of death or cardiovascular incidents brought to the attention of the FDA is beyond the scope of this review. However, it is fair to say that the system of reporting does not necessarily lead to productive scientific scrutiny since the quality of the data and the confounding treatments make it hard to make conclusions. These reports also have to be considered in the context of the background risk of sudden cardiac death and cardiovascular disease in the general population. The risk of sudden cardiac death is poorly understood, and estimates in young children and adolescents vary from 1.1 to 13.8 per 100,000 per year. It is usually associated with cardiomyopathy, primary disorders of cardiac conduction or congenital heart disease. The most common cardiac lesions found with sudden cardiac death include hypertrophic and other less common cardiomyopathies, coronary artery anomalies, long QT syndrome, Wolff-Parkinson-White syndrome and ventricular arrhythmias. Unfortunately, we do not have a good handle on the real number of children actually taking stimulants or dying suddenly while taking stimulants. Therefore, without good data for either numerator or denominator, we cannot determine the effect of stimulants on sudden death rates.

In the Clinic

Given the new concerns, there are several steps that neurologists might take to protect their patients and reduce their potential liability. Obviously, it is critical to begin with a thorough history and physical examination. The patient history should include questions about fainting or dizziness, chest pain or shortness of breath, easy fatigability compared to peers, palpitations, tachycardia, irregular heart beat, history of heart murmur of other heart problems. Family history should target sudden or unexplained death under age 35, especially if associated with exercise, long QT syndrome, Wolff-Parkinson-White syndrome or similar conditions, or any hypertrophic cardiomyopathy. The physical exam should document any abnormal heart murmur or other cardiovascular abnormalities including hypertension and irregular or rapid heart rhythm.

If an EEG is performed, it should include an EKG channel, and one needs to address rate, rhythm and corrected QT interval in the report. It is unclear at this time whether an electrocardiogram is necessary as a baseline prior to starting stimulants. Certainly, a full 12 channel EKG can identify cardiovascular problems including long QT syndrome, Wolff-Parkinson-White and hypertrophic cardiomyopathy, but the risk-benefit ratio is unclear in an otherwise healthy population without any historical or physical alarms. Whether or not the neurologist obtains a baseline EKG, there is no indication for repeated studies in the absence of cardiac symptoms.

There is also no reason to obtain routine cardiology consultations in low-risk individuals without significant personal or family history or physical findings as described above. For patients currently taking stimulants, it is important to make sure that the cardiovascular history is documented, physical exam reviewed, and EKG considered if not previously done. Finally, it is reasonable to re-evaluate with the family the purpose of medical treatment, the risks and alternatives to current therapy, and the real risks associated with not taking medication. It is easy to forget that overwhelming evidence has accumulated that untreated ADHD carries significant risk of academic failure, social disability, accidental injury, poor driving, tobacco and substance abuse and mental health problems.

Worth the Risk

It is important to keep in mind that ADHD is a public health problem of importance which affects five to seven percent of school age children and three to five percent of adults. Estimates of the adverse impact of ADHD run into the billions of dollars, and the emotional impact on a child’s self-esteem and reduced learning potential defy accounting. Furthermore, there is no scientific controversy on the ability of pharmacological intervention to reduce the core deficits of the disorder. Stated simply: drugs work, and stimulants work best.

The MTA study (National Institutes of Mental Health’s Multimodal Treatment Study of ADD) demonstrated elegantly that treatment with stimulants was clearly effective in improving the symptoms of inattentiveness, hyperactivity and impulsivity—especially when prescribed by specialists and when combined with behavioral interventions. Improvements went beyond the ADHD symptoms, and included improvement in scholastic achievement scores, better reading scores, higher social status in the classroom and more effective parenting. Furthermore, results of many carefully designed clinical trials have shown that stimulants are more often effective than other medical approaches with non-stimulants like atomoxetine or modafinil, but the effect size is greater. In other words, methylphenidate or amphetamine compounds work 80 percent or more of the time compared to 50 to 60 percent with non-stimulants, and they are better at producing a standardized amount of change as well.

So, what is the practicing neurologist to do? Perhaps the best advice is: be informed, be compassionate, be willing to talk to your patients, and don’t lose your prescription pad.

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