JPPT | Invited Commentary

Five Steps to Improve Cardiac Safety of Attention Deficit Hyperactivity Disorder Treatment

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ABBREVIATIONS ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; CDC, US Centers for Disease Control and Prevention; CVD, cardiovascular disease; DBP, diastolic blood pressure; ED, eating disorder; HR, heart rate

KEYWORDS amphetamine salts; atomoxetine; attention deficit hyperactivity disorder; cardiovascular disease; central nervous system stimulants; methylphenidate; viloxazine

J Pediatr Pharmacol Ther 2024;29(6):670–673

DOI: 10.5863/1551-6776-29.6.670

Introduction

Attention deficit/hyperactivity disorder (ADHD) medication prescribing is increasing in children and adults according to a US Centers for Disease Control and Prevention (CDC) analysis of prescription stimulant fills before and during the COVID-19 pandemic, with rates of ≥1 prescription stimulant fill(s) increasing from 3.6% in 2016 to 4.1% in 2021. Among females ages 15 to 44 and males ages 25 to 44 years, rates increased by more than 10% during 2020 to 2021.[1] Increased prescribing of stimulants, namely methylphenidate, dexmethylphenidate, mixed amphetamine salts, and lisdexamfetamine, has raised questions among patients, their families, and treatment teams regarding their safe use. Although the therapeutic benefits of stimulant treatment in children with ADHD to facilitate healthy growth and development into adolescence are well established, studies evaluating the long-term risk of cardiovascular disease (CVD) have been limited until now.[2,3]

Cortese and Fava[4] provide an excellent review and editorial commentary on the cardiovascular risk of ADHD medications, with patient-specific recommendations to support clinical decision-making. We agree and seek to build on their recommendations by highlighting findings from both Dalsgaard and colleagues[5] and Zhang et al[3] and pointing out additional patient-specific risk factors for CVD that should be considered, including consideration of co-occurring eating disorders or cannabis use disorder. Further, we point out the dose-related nature of cardiovascular risk associated with ADHD medications and remind clinicians that implementing adjunctive behavioral interventions for ADHD has been shown to decrease the effective stimulant dose, ultimately decreasing cardiovascular risk.[6] Indeed, the American Academy of Pediatrics ADHD Guidelines recommend behavioral treatment along with medications for school-aged children with ADHD, adding that benefit from consistently applied behavioral therapies tend to persist, whereas the positive effects of medications cease when medications stop. Additionally, teachers and caregivers report positive outcomes for consistently applied behavioral interventions.[7]

Key Findings from Dalsgaard et al and Zhang et al

Dalsgaard et al[5] prospectively monitored children born between 1990 and 1999 with ADHD (n = 8300) during 9.5 years and found the use of stimulants (amphetamine, dexamphetamine, methylphenidate) increased the risk of a cardiovascular event 2-fold (adjusted heart rate [HR], 2.20 [2.15–2.24]). Although cardiovascular events were rare (n = 111), they occurred twice as often in children with ADHD taking stimulant compared with those not taking stimulant. Hypertension and arrhythmias were the most common cardiovascular events reported. Children with ADHD previously treated with high doses (>30 mg/day of methylphenidate) were 2.2 times more likely to experience a cardiovascular event compared with children treated with lower doses.[5]

Zhang and colleagues[5] evaluated the association between cumulative, long-term (up to 14 years) use of ADHD medications and risk of CVD in a Swedish nationwide nested case-control study in individuals ages 6 to 64 years with ADHD. Cases with ADHD and CVD at baseline (n = 10,388) were prospectively compared to controls with ADHD and without a CVD diagnosis at baseline (n = 51,672).[3] The study found that longer cumulative use of ADHD medication was associated with a statistically significant increased risk of CVD compared with nonuse. Risk increased rapidly during the first 3 years of medication use and then stabilized. Each additional year of ADHD medication use was associated with an average 4% increased risk, with an increased risk of 8% for the first 3 years of medication

use. Higher doses (i.e., >45 mg/day methylphenidate/lisdexamfetamine, >22.5 mg/day amphetamines, >120 mg/day atomoxetine) were associated with higher risk.[3] Specifically, greater risk of hypertension and arterial disease stood out with no significant increased risk for arrhythmia, heart failure, ischemic heart disease, thromboembolic disease, and cerebrovascular disease.[3]

Cardiovascular Risk Across ADHD Medications

Selecting a nonstimulant treatment for ADHD is not the solution for minimizing the cardiovascular risk of ADHD treatment. Stimulant treatment is superior in effectiveness to both nonstimulant noradrenergic reuptake inhibitors and alpha-2 adrenergic agonists.[2,7] Although nonstimulants are often perceived as benign alternatives to stimulants, it is important to acknowledge their cardiovascular risk. Selective norepinephrine reuptake inhibitors, atomoxetine and viloxazine, are associated with clinically relevant increases in HR and diastolic blood pressure (DBP).[8,9] In clinical trials, viloxazine increased HR by ≥20 bpm in ~30% of children and adolescents, compared with ~15% of those who received placebo in a dose-dependent fashion. Among adolescents treated with viloxazine 400 mg daily, 25% had a ≥15 mm Hg increase in DBP at any time in the clinical trial compared with 13% in the placebo group.[8]

A large placebo-controlled study comparing osmotic release oral system methylphenidate and atomoxetine in children with ADHD showed atomoxetine was associated with a significantly increased HR compared with placebo, but methylphenidate did not increase HR more than placebo.[9] Meta-analytic evidence from randomized clinical trials shows that amphetamine or atomoxetine use is associated with statistically significant but, on average, small increases in systolic and DBP (≤5 mm Hg) and HR (≤10 bpm), and methylphenidate may lead to small increases in blood pressure.[10] Observational longer-term studies have provided further insights. For instance, in a study comparing youths with ADHD treated with methylphenidate for at least 2 years and a medication-naive ADHD control group, a BP indicative of hypertension was observed in 12.2% of the methylphenidate group and in 9.6% of the control group, with overlapping CIs.[11] Sustained increases in HR and blood pressure might result in left ventricular hypertrophy and an elevated risk of myocardial infarction.[4]

In an open-label, extension study (N = 207) the cardiovascular risk of dexmethylphenidate (5–20 mg/day) was compared to that of guanfacine (1–3 mg/day). Overall, dexmethylphenidate was associated with a small increased systolic blood pressure, whereas guanfacine was associated with decreased blood pressure and HR. Notably, both returned to baseline during the 1-year open-label extension phase.[12] Although further head-to-head studies are needed to assess the impact of clonidine and guanfacine on the cardiovascular health of individuals with ADHD, risk has been described based on pharmacodynamic effects. As potent stimulators of central alpha-2 adrenergic receptors, resulting in decreased release of norepinephrine, they may cause/exacerbate sinus bradycardia/atrioventricular block.[13]

Cardiovascular Risk With a Co-occurring Eating Disorder or Substance Use Disorder

It is estimated that ~20% of children with ADHD will develop an eating disorder (ED), most frequently binge ED, followed by bulimia nervosa, and lastly anorexia nervosa (AN).[14] Stimulant treatment of ADHD in persons with an uncontrolled ED increases the risk of CVD. Structural and functional abnormalities associated with AN pose the greatest risk of cardiovascular complications, followed by electrolyte abnormalities in persons with bulimia nervosa or the purging type of AN. Obesity is a well-established risk factor for CVD in persons with binge ED.[14] Additionally, among adolescents and young adults with an ED, about 60% will develop a substance use disorder in their lifetime.[15] Nicotine, alcohol, cannabis, and stimulant use disorders have the highest lifetime prevalence among this group.[16,17] Among youth and adults with ADHD, cannabis, alcohol, and nicotine are the most misused substances.[17,18]

Although the cardiovascular risks of nicotine and alcohol are often considered by consumers and health care professionals alike, the risks of cannabis may be underappreciated. Cannabis has proinflammatory properties that may interfere with physiologic autonomic nervous system control, resulting in clinically meaningful decreased HR variability.[18] The cardiovascular effects of cannabis are both acute and chronic. Acutely, the psychoactive component of cannabis, delta-9-THC, is associated with tachycardia, hypertension, platelet activation, and endothelial dysfunction.[18] Chronically, cannabis increases the risk of CVD, cardiomyopathy, and arrhythmias.[18,19] A 2024 study using CDC data shows 25% higher rates of myocardial infarction and 42% greater risk of stroke in persons smoking cannabis daily compared with nonsmokers.[19]

Implications for Practice

New information on the long-term cardiovascular risk of ADHD medications should not prevent health care providers from continuing to prescribe stimulants for well-diagnosed ADHD. After all, stimulant medications are the most effective treatment and can improve educational, occupational, and social outcomes. In addition to improving therapeutic outcomes, observational studies show stimulant medication initiation in persons with ADHD has been shown to significantly decrease hospitalizations, and lower mortality in particular for unnatural causes such as accidental death or suicide.[20,21]

We recommend the following 5 steps to increase the cardiac safety of ADHD medication:

1. Provide patient and family education on 2 to 3 specific goals of ADHD treatment, benefits of stimulant therapy for ADHD, and risks of treatment, including risk of adverse cardiac effects and need for regular monitoring. Reevaluate pharmacotherapy if treatment goals are not met.
2. Screen each child with ADHD for factors that increase CVD risk before starting stimulant trial (e.g., preexisting structural cardiac abnormalities, eating disorder, active nicotine, cannabis, or stimulant use disorder).
3. Implement parent training (education on ADHD) and a behavioral therapy plan (rewards for desired behavior and structured limit setting)[6,7] along with medication in an attempt to achieve treatment goals with lowest medication dose.
4. Provide family and caregiver support to ensure the success of the behavioral therapy plan. Initial trial of methylphenidate preferred versus amphetamines or noradrenergic reuptake inhibitors because of the high efficacy and overall lower risk of CVD.
5. Monitor pulse and blood pressure at baseline and regularly (e.g., once weekly) during treatment. Report persistent increases in pulse >10 bpm or systolic or DBP > 10 mm Hg to prescriber. Reevaluate benefits and risks of ongoing stimulant treatment annually.

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Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Ethical Approval and Informed Consent. Not applicable.

Submitted. April 4, 2024

Accepted. April 4, 2024

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