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Evaluation and Management of Elevated Blood Pressure in Children and Adolescents with Attention Deficit Hyperactivity Disorder

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Abstract

Purpose of Review To understand the impact of attention deficit hyperactivity disorder (ADHD) and its medications on blood pressure (BP) in children and adolescents and provide recommendations for management of elevated BP in children and adolescents with ADHD.

Recent Findings ADHD medications have cardiovascular effects including elevated BP. However, the bulk of the evidence indicates that stimulants and other ADHD medications are safe and do not cause severe cardiovascular diseases. BP should be assessed carefully at the time of ADHD diagnosis, because some behavioral changes similar to ADHD may be associated with hypertension.

Summary ADHD medications appear to be safe. However, their long-term impact on the cardiovascular system is not clearly understood and needs further investigation. BP should be monitored regularly during ADHD pharmacotherapy in order to optimize the management of both conditions.

Keywords ADHD · Pediatric hypertension · Elevated blood pressure · Stimulants · Cardiovascular disease

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood, affecting up to 12% of all children worldwide [1–3]. Pharmacological treatment with stimulants such as methylphenidate and amphetamines is well established for the treatment of ADHD. Other non-stimulant agents used are atomoxetine, alpha-2 adrenergic agonists, and antidepressants. These medications affect not only the central nervous system but also the cardiovascular system. Numerous studies have shown that stimulants and atomoxetine increase blood pressure and heart rate. This is of particular concern in the context of the increasing prevalence of hypertension (3–5%) and elevated blood pressure (10–12%) in children and adolescents, mainly due to the obesity epidemic [4••, 5]. Pediatric providers and pediatric hypertension experts have been seeing more patients with elevated blood pressure in clinics [6, 7], and more ADHD patients have been referred for evaluation of elevated blood pressure [8, 9]. Here, we review the evaluation and management of elevated blood pressure in children and adolescents with ADHD.

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ADHD

Attention deficit hyperactivity disorder (ADHD) presents in childhood with symptoms of hyperactivity, impulsivity, and/or inattention. To meet criteria for ADHD, the symptoms must be present in multiple settings for at least 6 months and show clear evidence of interference with or reduction of the quality of social, academic, or occupational function. The diagnosis of ADHD requires that the child meet the criteria defined by the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-5) [10]. In Europe, the diagnosis of ADHD is defined by either DSM-5 or ICD10. The diagnosis

of ADHD requires comprehensive medical, developmental, educational, and psychosocial evaluation.

The prevalence of ADHD in school-age children in the USA is between 8 and 11% and is increasing [11–13]. ADHD is more common in boys than in girls. Emotional and behavioral disorders commonly coexist with ADHD, including conduct disorder, oppositional defiant disorder, depression, anxiety disorder, and learning disabilities [14]. Some genetic syndromes such as Fragile-X syndrome, DiGeorge syndrome, Turner syndrome, tuberous sclerosis, neurofibromatosis, Williams syndrome, and Klinefelter syndrome have higher prevalence of ADHD [15–17]. Children with congenital heart disease (CHD) also have higher prevalence of ADHD [18–22]. In a retrospective nationwide population-based case-control study in Taiwan, the congenital heart disease group had an increased risk of developing ADHD and autism spectrum disorders [19]. In another study, Demaso et al. [18] studied adolescents with single-ventricle congenital heart diseases who underwent the Fontan procedure (CHD group), finding a greater than 5-fold increased risk of lifetime ADHD and anxiety compared with adolescents without medical conditions. The specific etiologies responsible for the high incidence of ADHD in CHD are not clear, but hypoxia and low cardiac output might contribute to these findings.

ADHD and Blood Pressure

The prevalence of elevated blood pressure in children and adolescents with ADHD appears to be the same as in the general population. Using National Health and Nutrition Survey data, Hailpern et al. [9] investigated blood pressure and CV risk factors in children with ADHD. Data were available for 4907 children aged 12–18 years with and without the diagnosis of ADHD. Of this total cohort, 383 (10.7%) had a diagnosis of ADHD, and 111 (3.4%) were on stimulants. Hypertension was found in 3.57%, 2.06%, and 2.69% of the children with ADHD on stimulants, with ADHD without stimulants, and without ADHD, respectively. Prehypertension was found in 13.79%, 13.74%, and 12.19% of the children in these groups, respectively. The study suggests that the prevalence of elevated BP does not differ according to the diagnosis of ADHD or the use of stimulants. In contrast, a study of Canadian children by Grisaru et al. [8] found a higher prevalence of casual elevated blood pressure and hypertension in children with ADHD when compared with control data from the Canadian Health Measures Survey (CHMS). These investigators examined the office and ambulatory blood pressure status of 55 children with a diagnosis of ADHD who were currently on ADHD medications. The frequency of elevated blood pressure and hypertension in their ADHD population was 9% and 5%, respectively, compared with 3% and 2% in the CHMS data from 2012 to 2013. However, review of the ambulatory blood pressure monitoring (ABPM) studies showed that none of those with office pressures in the elevated or hypertensive range demonstrated hypertension on ABPM. White-coat hypertension was diagnosed in 5.5% and masked hypertension in 3.6%. They also noted a high prevalence of blunted nocturnal dipping and sleep disturbance [8].

Adams et al. [23] found that children referred for elevated blood pressure and found to have primary hypertension were more likely to have ADHD and learning disabilities than those in whom hypertension was excluded. Twenty percent of those with hypertension had ADHD, versus 7% of those found to be normotensive. However, regardless of ADHD treatment, children with hypertension had a four-fold higher odds ratio of learning disabilities compared with children without hypertension. Of note, the diagnosis of ADHD was inferred from treatment with medications typically used for this disorder. The National Longitudinal Study of Adolescent Health, a population based survey of over 12,000 adolescents across the USA from 1995 to 2009, found that childhood history of hyperactive/impulsive and/or inattentive symptoms was linked with hypertension; however, the association did not persist after controlling for BMI [24].

In a few cases, behavioral symptoms associated with ADHD may be early manifestations of renovascular hypertension or pheochromocytoma. Krause et al. [25] reported that five out of eleven children with renovascular hypertension had behavioral changes prior to the diagnosis of hypertension; these included restlessness, sleep disturbances, temper tantrums, hyperactivity, aggressive behavior, and attention deficit. Correction of renovascular hypertension led to complete or partial resolution of the behavioral changes. Two articles reported association between ADHD and the diagnosis of pheochromocytoma/paraganglioma in pediatric patients [26, 27•]. Haws et al. described two patients with pheochromocytoma who presented with behavioral symptoms similar to those of ADHD. One patient had an inability to concentrate, poor school performance, and hyperactivity. He was diagnosed with ADHD and was on dextroamphetamine/amphetamine prior to the diagnosis of pheochromocytoma. The second patient had a two-year history of difficulty in concentrating, anxiety, and inability to remain seated. Both patients' behavioral symptoms resolved after the pheochromocytoma was removed.

Cardiovascular Effects of ADHD Medications

Two-thirds of children with a current ADHD diagnosis are treated with medications [28], including stimulants and non-stimulants. The stimulants are methylphenidate and various amphetamine preparations (mixed amphetamine salts and lisdexamfetamine). The non-stimulants include two alpha-

adrenergic agonists (clonidine and guanfacine) as well as the norepinephrine reuptake inhibitor atomoxetine. Increases in blood pressure and heart rate related to the use of methylphenidate, amphetamines, and atomoxetine for ADHD are well documented. The average increases in systolic blood pressure, diastolic blood pressure, and heart rate are 3–8 mmHg, 2–14 mmHg, and 3–10 beats per minute, respectively [29–31]. The effects of stimulants on hemodynamics may be dose dependent [32].

In a small study of 11 children, Samuels et al. [33] investigated the cardiovascular impact of stimulants by performing 24-h ABPM while patients were on and off medications. The children studied were 5–15 years old and were on a stable dose of stimulants for ADHD. Each participant received either active treatment or placebo for 3 days, then underwent a 24-h ABPM, then switched to the alternate condition for 3 days and repeated a 24-h ABPM. The study showed that virtually all values measured during ABPM were higher during active treatment compared with placebo. Overall diastolic BP, awake diastolic BP, and heart rate were significantly elevated during active treatment compared with placebo period. The rate-pressure product (RRP) (SBP × HR, an index of myocardial oxygen demand) was also significantly elevated. Grisaru et al. [34] compared ABPM findings in children with and without ADHD referred for evaluation of elevated blood pressures. This large retrospective included 48 children with ADHD, 39 of whom were on medication and 179 without ADHD. Analysis showed that the children with ADHD were significantly more likely to manifest elevated awake systolic load, i.e., an increased percentage of awake systolic blood pressure readings above the threshold compared with those without ADHD [34].

ADHD is typically diagnosed during childhood, but it continues into adolescence and adulthood in up to 65% of cases, and pharmacotherapy can be lifelong [35, 36]. Studies of the long-term outcomes of pharmacotherapy are limited. The Multimodal Treatment Study of Children with ADHD performed a multi-site, randomized, controlled clinical trial to investigate the risk of developing abnormalities in blood pressure or heart rate over 10 years [37]. A total of 579 children aged 7 to 9 years were studied. No treatment effect on either systolic or diastolic BP was found. There was no evidence that stimulants increased the risk of pre-hypertension or hypertension. However, stimulants had a persistent adrenergic effect on heart rate if continued [37]. Conzelmann et al. [38] investigated the long-term cardiovascular safety of methylphenidate in 1042 children aged 7 to 17 years with ADHD in a child and adolescent psychiatric practice in Southern Germany between 1998 and 2010. They found that systolic and diastolic blood pressure percentiles were actually decreased after stimulant treatment.

There has been concern that ADHD medications, and particularly stimulants, may affect cardiac autonomic function and predispose individuals to arrhythmias or sudden death. In a cross-sectional study, Kelly et al. [39] compared 85 children and adolescents with ADHD on stimulants with a control group of 53 siblings without ADHD using measures of endothelial function, arterial stiffness, and heart rate variability. The results demonstrated evidence of increased sympathetic tone as well as arterial stiffening in those with ADHD, which was not affected by stimulant dose or cumulative exposure. The impact of these changes over time is not known.

Stimulants are also known to prolong the corrected QT interval (QTc), which may increase the risk of ventricular tachycardia [40••, 41•]. The mechanism of QTc prolongation by stimulants is not known, but the effect is usually modest. The main concern is that slow metabolizers may have significant QTc prolongation and have high risk of ventricular tachycardia. However, most studies were short term, and the long-term outcome needs to be elucidated [42, 43].

A recent review identified nine population-based studies on stimulants and pediatric cardiovascular risk, which present a mixed picture on the safety of these agents [44•]. A case-control study comparing sudden unexpected deaths in youth using stimulants to a matched group of motor vehicle passenger deaths found a 7.4-fold increase in the odds of sudden death with simulant use [45]. Winterstein et al. showed that stimulant use increased the risk of cardiac-related emergency department visits by 20%, and concurrent use of antidepressants or antipsychotics further increased the risk of cardiac-related ED visits [46, 47]. On the other hand, two large-scale retrospective cohort studies found that use of ADHD medications was not associated with an increased risk of cardiovascular events [48, 49].

ADHD Medications

Methylphenidate is a dopamine and norepinephrine reuptake inhibitor. It is known to increase heart rate and blood pressure. Ventricular arrhythmias have been reported. Cardiac function can be decreased in overdose. The non-cardiac side effects of methylphenidate include decreased appetite, sleep disturbance, nausea, vomiting, abdominal pain, and headache. Polymorphisms in several genes associated with cardiovascular diseases may impact changes in blood pressure caused by methylphenidate in children with ADHD [50].

Mixed amphetamine salts and other amphetamine preparations are adrenergic agonists that act both centrally and peripherally. Centrally, they stimulate release of norepinephrine from stores and block dopamine reuptake, improving patients' focus. Peripherally, these agents have sympathomimetic effects mediated by beta- and alpha-receptors. The peripheral action increases heart rate and blood pressure. Sleep disturbances appear to be worse in patients taking amphetamine compared with methylphenidate.

Atomoxetine is a selective norepinephrine reuptake inhibitor. It inhibits the presynaptic norepinephrine transporter without inhibiting dopamine reuptake. Most pediatric patients develop mild to modest increases in BP and HR, but 8–12% of patients experienced more pronounced increases in BP and HR [51]. The non-cardiac side effects of atomoxetine are decreased appetite, nausea, and abdominal pain. Somnolence is more common than insomnia. There may be a lower risk of abuse compared with amphetamines. The dose may need to be adjusted for patients who receive CYP2D6 inhibitors or have reduced atomoxetine metabolism via the CYP2DG or CYP2C19 enzyme systems. These patients may achieve higher serum levels of atomoxetine, which may cause longer QTc intervals [43].

Guanfacine and clonidine are alpha-2 adrenergic agonists. They decrease peripheral vascular resistance and usually decrease BP and HR. They have no effect on the ECG, but may cause mild sedation, and are known to cause rebound hypertension with abrupt cessation. They are often added to a medication regimen for significant insomnia or other psychological issues such as oppositional or aggressive behavior.

Bupropion is a norepinephrine and dopamine reuptake inhibitor. It increases BP and causes cardiac toxicity in cases of overdose in adults. Its non-cardiac side effects include seizure, agitation, insomnia, dry mouth, nausea, vomiting, and headache.

Overdosing

Increased use of ADHD medications poses a risk of unintentional or intentional overdose or misuse, affecting children of all ages. National Poison Data System data from 2000 through 2014 showed that 156,365 exposures were reported. Overall, exposures have increased over the years. Methylphenidate and amphetamine medications account for the majority of exposures [52•]. Similar results were found in Australia [53]. During the period from 2004 to 2014, there was a 210% increase in intentional exposures to methylphenidate, and illicit use increased by 429%. Ninety-three percent of patients required hospitalization. Stimulant medication overdose can result in a variety of symptoms including mydriasis, tremor, agitation, tachycardia, hyperreflexia, confusion, hallucinations, hyperthermia, and status epilepticus [52•, 53].

Conclusions/Recommendations on Elevated Blood Pressure in Children and Adolescents with ADHD

Prior to pharmacotherapy, all patients with ADHD should undergo physical examination and obtain their baseline height, weight, blood pressure, and heart rate. If BP is elevated, we recommend following the American Academy of Pediatrics (AAP) "Clinical Practice Guideline for screening and management of high blood pressure in children and adolescents" [4••]. The European Network for Hyperkinetic Disorders and the NICE guidelines state similar recommendations [54, 55]. If the patient's BP is persistently elevated, he/she should be referred to a pediatric hypertension specialist for further evaluation before initiating treatment of ADHD.

Patients on pharmacotherapy for ADHD should be seen in a clinic by the specialist treating ADHD every 3 to 6 months to monitor side effects and medication efficacy [55, 56]. Blood pressure should be measured manually with proper technique prior to treatment and at each visit. If a patient taking ADHD medication has sustained resting tachycardia (more than 120 beats per minute), arrhythmia, or systolic blood pressure $\geq$95th percentile or $\geq$ 130/80 (or a clinically significant increase) on two or three occasions, then their dose may need to be reduced; those with elevated pressures should be referred to a pediatric hypertension specialist [57]. We recommend that patients taking ADHD medications who develop elevated blood pressure undergo a 24-h ABPM. If sustained hypertension is confirmed, then the pediatric hypertension specialist and providers treating ADHD should communicate about alternatives and dosing or trial-off of ADHD medications [58•]. Discontinuation of ADHD medications is usually not an option for most patients and may be quite disruptive for patients and their families, even for a limited period to allow evaluation of the elevated pressure. Given that the impact on the cardiovascular system may not be large, we recommend that patients with ADHD or on ADHD medications be treated the same as other patients and that other etiologies of hypertension should be considered, particularly if the elevation is more than typically seen with ADHD medication exposure.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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