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Cardiovascular Safety of Stimulants in Children: Findings from Recent Population-Based Cohort Studies

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Abstract The past decade has seen a heated debate over the cardiac safety of central nervous system stimulants in the treatment of ADHD. This review discusses five controlled population-based studies that investigated this risk in children in the United States. All studies utilized administrative claims data of private or public insurance to compare risk of stimulant use to non-use. Two studies with smaller sample size lacked the ability to investigate serious events but report a slightly increased risk of emergency department visits attributed to cardiac symptoms such as tachycardia or palpitation. Three studies that enrolled more than one million patients found no association between stimulants and composite endpoints of sudden cardiac death, myocardial infarction, stroke and ventricular arrhythmia. The studies concur that background rates of serious cardiovascular events in children are extremely small. No study exceeded an average follow-up of two years, prohibiting inferences about long-term effects of stimulants.

Keywords Attention deficit hyperactivity deficit · ADHD · Central nervous system safety · Drug safety · Cardiovascular risk · Stimulants · Children · Pharmacoepidemiology · Psychiatry

Introduction

The safety of central nervous system stimulants (stimulants) has been an involved debate over the past decade. Stimulants are widely used in the treatment of attention deficit hyperactivity disorder (ADHD), resulting in drug exposure of millions of children and adolescents, as well as an increasing number of adults [1]. Parallel to the increasing use of stimulants have been spontaneous reports of adverse events, including major cardiovascular events such as stroke and sudden cardiac death. Twenty international reports of sudden death resulted in the withdrawal of Adderall XR from the Canadian market in February 2005; a decision that was revoked six months later. The Drug Safety and Risk Management Advisory Committee of the US Food and Drug Administration (FDA) voted in February 2006 to recommend a black-box warning describing the cardiovascular risks of stimulant drugs used to treat attention-deficit/hyperactivity disorder (ADHD) [2]. In response, the Pediatric Advisory Committee of the FDA suggested that a black-box warning may not be warranted [3]. The committee argued that a black box is meant for situations where the risk/benefit analysis would suggest not using the medication, which is not applicable to stimulants, given the strong evidence on treatment effectiveness and the weak evidence on risk.

The Drug Safety Advisory Committee's decision was based on the established propensity of sympathomimetic agents to raise blood pressure and heart rate [4–8], the history of serious adverse effects associated with other members of this drug class, such as methamphetamine and phenylpropanolamine [9], and the rapid increase in stimulant use, suggesting a massive public health impact if the risk were confirmed [2]. This notwithstanding, the only available evidence on severe cardiovascular events were case reports, which deliver no proof of causality, especially because some cases had congenital heart disease. Moreover, background incidence rates of cardiac sudden death in the general population were slightly higher when compared with the rate of spontaneous reports per estimated number of children exposed to Adderall according to the FDA. Controlled clinical trial evidence of the cardiac risk of stimulants approved for ADHD treatment consists of data demonstrating an increase in blood pressure and heart rate, which is typically described as mild, of short duration, and responsive to dosing or timing adjustments [4–8].

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Table 1 Study endpoints and risk estimates in five population-based studies on stimulant cardiac risk

	Study population	Primary study endpoints	Total number of events	Estimated incidence per100,000 years of stimulant use	Estimated relative risk (95 % CI)
Florida Medicaid Study [10] (n=55,383)	Children and adolescents age 3 to 20 years eligible for Florida Medicaid, newly diagnosed with ADHD and without exposure to stimulants within six months before study entry	ED visits for AMI, stroke, hypertension, angina, aortic or thoracic aneurysm, arrhythmias, syncope, tachycardia, or palpitation	1,091	1,090	1.20 (1.04–1.38)
Pennsylvania Study [12] (n=1,059,138)	Children age 3 to 17 years eligible for selected private or public insurance	ED or hospital visits for sudden death or ventricular arrhythmia	Not reported	0.6	1.60 (0.19-13.60)
Columbia Study [13] (n=171,126)	Children and adolescents age 6 to 21 eligible for private insurance, without known cardiovascular risk factors, with a diagnosis of ADHD, and no exposure to stimulants within six months before study entry	ED or hospital visit for angina, cardiac dysrhythmia, or transient cerebral ischemia	162	33.6	0.69 (0.42-1.12)
		ED or hospital visit for tachycardia, palpitations, or syncope	312	112.4	1.18 (0.83-1.66)
Vanderbilt Study [14] (n=1,200,438)	Children and adolescents age 2 to 24 years eligible for selected public or private insurance, without serious life-threatening illness	Sudden cardiac death, AMI, stroke	81	2.3	0.75 (0.31-1.85)
Florida II Study [15] (n=1,219,847)	Children and adolescents age 3 to 18 eligible for Medicaid in 28 states, newly diagnosed with ADHD, adjustment reaction, disturbance of conduct or other, mixed or unspecified emotional disturbance, and no exposure to stimulants within six months before study entry	Sudden cardiac death, AMI, stroke	66	2.2	0.62 (0.27-1.44)
		Same endpoint in high-risk patients	26	76.7	1.02 (0.28-3.69)
		Sudden cardiac death, AMI, stroke, arrhythmia	95	3.7	0.74 (0.38-1.46)

Five large population-based cohort studies in children and adolescents have been conducted since the initial controversy over stimulants safety, arriving at similar conclusions. The results of these studies are presented and discussed in the following paragraphs.

The Florida Medicaid Study

Our research team started in 2005 to assemble a population-based cohort from Florida Medicaid billing data (1994–2004), cross-linked to Florid Death Registry data [10]. The cohort was composed of all youth 3 to 20 years of age who were newly diagnosed with ADHD, resulting in 55,383 children and 124,932 person-years of follow-up. Each month of follow-up was classified according to stimulant claims (methylphenidate, amphetamines, and pemoline) as current use (active stimulant claim), former use (time after periods of current use), or nonuse (time preceding the first stimulant claim). We chose a wide range of study endpoints including (1) cardiac death, (2) first hospital admission for cardiac causes defined as principal diagnosis of acute myocardial infarction, stroke, hypertensive disease, angina, aortic or thoracic aneurysm, or arrhythmias, or (3) first emergency department visit for cardiac causes defined as for hospital admissions or for cardiac symptoms including syncope, tachycardia, or palpitation. We found five deaths due to cardiac causes, none of which occurred during 42,612 person-years of stimulant use. Hospital admissions for cardiac cause occurred for 27 children, too few for formal inferential comparisons. A total of 1091 children visited the emergency department for cardiac causes (8.7 per 1000 person-years). Current stimulant use was associated with a 20 % increase in the hazard for emergency department (95 % confidence interval [CI] 1.04–1.38) visits when compared with nonuse (Table 1). The analysis was adjusted for a variety of cardiac risk factors, socio-demographic characteristics, and concomitant use of other drugs with adrenergic side effects.

Because case reports have suggested greater cardiovascular effects for mixed amphetamine salts, we used the same cohort for a comparative safety study on cardiovascular symptoms (ED visits) [11]. A total of 12,338 youth contributed 11,110 years of observation while receiving amphetamines, and 18,238 youth received methylphenidate for 17,175 years. After adjusting for covariates the risk for ED visits was similar among methylphenidate and amphetamine users, with an adjusted hazard ratio of 1.01 (CI 0.80–1.28)

for periods of current use. Likewise, periods of former use of methylphenidate versus amphetamine showed a similar risk (adjusted HR=0.95, CI 0.73–1.25).

The Pennsylvania Study

This study conducted by researchers at the University of Pennsylvania was based on billing data from two administrative databases representing private and public insurance [12]. Similar to the Florida study, the cohort included children aged 3 to 17, but did not require presence of a diagnosis for ADHD. A total of 241,417 stimulant users were matched to up to four non-users on data source, gender, state, and age. The authors chose a narrower primary endpoint of sudden cardiac death of ventricular arrhythmia and validated a subsample of cases via medical chart review. Because of a large false positive rate in the validation subsample, the authors decided to restrict their analysis to cases that were validated, resulting in a very small incidence of the endpoints. Of note, the primary reason for false positives was erroneous attribution of trauma-related death to sudden cardiac death. The hazard ratio for the comparison of incident users versus non-users for the primary endpoint was 1.60 (CI 0.19-13.60). The authors concluded correctly that the small incidence rate resulted in limited ability to rule out increases in cardiac risk.

The Columbia Study

This study, funded by the National Institute of Mental Health, used a cohort of 171,126 privately insured children and adolescents (age 6–21) without known cardiovascular risk factors, with a diagnosis of ADHD, and no exposure to stimulants within six months before study entry [13]. Follow-up time after ADHD diagnosis was classified according to pharmacy claims for methylphenidate or mixed amphetamine salts as current, past, and no stimulant use. The study had been planned to investigate three types of events. Severe cardiovascular events (acute myocardial infarction, stroke, ischemic heart disease or sudden death) occurred in only one patient. Hence, the analysis was focused on the less severe endpoints, including emergency department or inpatient diagnosis of 1) angina pectoris, cardiac dysrhythmia, or transient cerebral ischemia, or 2) tachycardia, palpitations, or syncope.

The study found incidence rates of 0.92 new cardiac events and 3.08 new cardiac symptoms per 1,000,000 days of current stimulant use. Compared to no stimulant use, the adjusted odds ratio of cardiac events was 0.69 (CI 0.42–1.12) during current stimulant use and 1.18 (CI 0.83–1.66) during past stimulant use. The corresponding adjusted odds ratios for cardiac symptoms were 1.18 (CI 0.89–1.59) for current and 0.93 (CI 0.71–1.21) for past stimulant use. A direct comparison of methylphenidate versus amphetamine use showed no significant difference for cardiovascular symptoms (1.08, CI 0.66–1.79). All analyses were adjusted with an exposure propensity score including a variety of cardiovascular risk factors, adrenergic medications, socio-demographic characteristics, and receipt of well child visits as proxy for preventive care.

The Vanderbilt Study

This study, which was funded by the Agency for Healthcare Research and Quality (AHRQ) and the Food and Drug Administration (FDA), utilized billing data from two states' Medicaid programs, Kaiser Permanente California, and OptumInsight (private insurances) [14]. The study included 1,200,438 children and young adults between the ages of 2 and 24 years without serious life-threatening illness and 2,579,104 person-years of follow-up. A diagnosis of ADHD was not required. The authors chose a narrow endpoint of sudden cardiac death, acute myocardial infarction, and stroke from hospital claims or death certificates. Billing codes to ascertain these events were defined broadly, because potential cases were subjected to medical-record review. In 21 % of cases where records were not accessible, the authors used a validated set of billing codes. Of note, cardiac deaths were only included if secondary causes of death did not include certain trauma or illicit drug use. Like in the previous studies, stimulant use was categorized from pharmacy claims as current, former, or no use.

The authors found 81 cardiovascular events (3.1 per 100,000 person-years). Current users of ADHD drugs were not at increased risk for serious cardiovascular events (HR=0.75; CI 0.31-1.85) when compared to no use. Analyses were adjusted by an exposure propensity score, which included cardiac risk factors, psychiatric disorders, unintentional injuries, and socio-demographics. While the primary analysis was not restricted to new users of stimulants, a sensitivity analysis showed similar results with wider confidence intervals.

The Florida-II Study

This second stimulant safety study conducted by our research team, funded by AHRQ, enrolled 1,219,847 children and adolescents age 3 to 18 years and eligible for Medicaid fee-for-service benefits in 28 states (Medicaid Extract Files [MAX]) [15]. Study entry required a new diagnosis of ADHD or other psychiatric disorders commonly treated with stimulants (adjustment reaction, disturbance of conduct or other, mixed or unspecified emotional disturbance).

Similar to the Vanderbilt study we excluded children with severe disease such as post-transplant status or on dialysis, as well as those with claims indicating substance use. However,

we retained high-risk groups with similar stimulant utilization as low-risk children and conducted stratified analyses. The high-risk stratum included children with a diagnosis of malignant neoplasm, hereditary or acquired haemolytic and aplastic anaemia, HIV/AIDS, congenital heart disease or other congenital disease with vascular involvement, cardiomyopathy, valve disorders, or cerebrovascular disease. Also like previous studies we used pharmacy claims to classify stimulant exposure as current, former or no use.

The study's primary endpoint included stroke, myocardial infarction or sudden cardiac death and followed the validated claims data algorithm employed by the Vanderbilt study with one exception: for all qualifying cardiac deaths, we hand-reviewed secondary causes of death noted on death certificates and expanded the original list of exclusionary secondary causes related to trauma and illicit drug use. We further introduced a secondary endpoint that added hospitalizations for ventricular arrhythmia to the primary endpoint to capture potential severe chronotropic effects. For sensitivity analysis we furthermore introduced an additional set of censoring diagnoses involving trauma (e.g., head injury) or acute inflammatory heart disease, intracranial or severe viral infections, which may acutely increase the risk for cardiovascular events or stroke.

Our analysis found a total of 66 (95 including ventricular arrhythmia) events over 2,321,311 years of follow-up (2.8 per 100,000 patient-years). The odds ratio for current versus no stimulant use was 0.62 (CI 0.27 to 1.44). Twenty-six events occurred in high-risk patients (incidence rate 63 per 100,000 patient-years) with OR = 1.02 (CI 0.28 to 3.69). ORs for the secondary endpoint were similar to those for the primary endpoint (0.74, CI 0.38 to 1.46), as were estimates with injury censoring.

All analyses were adjusted with an exposure propensity score including socio-demographic characteristics, cardiac risk factors and drugs, and psychiatric diagnoses and psychotropic drugs. We furthermore included time-dependent covariates of concomitant adrenergic, antidepressant, or antipsychotic medication use and age.

Summary of Study Findings

Findings across the five reviewed population-based studies show impressive consistency. Stimulants show an association with emergency department visits for cardiac symptoms such as tachycardia, but no association with more severe cardiac events (Table 1). The former observation is consistent with clinical trial data on stimulant-induced increases in heart rate and blood pressure, which conceivably may cause sufficient concern to result in emergency care. Differences in reported incidence rates across studies likely result from varying definitions of study endpoints and the in- or exclusion of high-risk patients. Using the same endpoint definition, two of the three largest studies, Vanderbilt and Florida-II, report almost identical incidence rates and similar risk estimates (Table 1). Incidence estimates of the Pennsylvania study are smaller, not only because of a narrower endpoint definition, but also because the majority of cases were discarded after chart review validation of a subsample failed. Of note, stratified results in the Florida-II study illustrate the disproportional contribution of high-risk patients to cardiac event incidence rates and emphasize the importance of specific analysis that target this patient group. Investigation of this subgroup of patients, only reported in the Florida-II study, suggests no increased risk of stimulants, but confidence intervals are large due to small sample size and cannot exclude a three-fold increase in risk (upper limit of the 95 % confidence interval is 3.69).

Severe cardiac events have a standard definition in adult safety studies, referred to as MACE (major cardiovascular events) and include sudden cardiac death, stroke and myocardial infarction [16]. The operationalization of cardiac adverse events is more challenging in pediatric populations and with consideration of pharmacological properties of stimulants. A possible pathway of severe short-term effects of stimulant use is tachycardia-induced cardiomyopathy, a reversible form of cardiomyopathy that has been described in pediatric and adult patients [17, 18]. Controlling arrhythmias, which usually present as supraventricular or ventricular arrhythmia, and heart rate, usually results in rapid improvement in cardiac function with normalization of the ejection fraction within one to two weeks [19]. Depending on other conditions (e.g., extensive exercise, dehydration, underlying congenital heart disease) arrhythmia might result in cardiac death. Thus, while we used a more standard definition of severe cardiac events (the triad of cardiac death, stroke or AMI), stimulant pharmacologic action suggests that investigation of arrhythmias, and particularly ventricular arrhythmia, was critical. Fortunately, neither Florida-II or the MarketScan study found reason for concern when investigating arrhythmias.

Another potential pathway, which could not be addressed by any of the available studies, is the long-term effect of subtle increases in heart rate and blood pressure. The average follow-up time in the two largest studies, Vanderbilt and Florida-II, was less than two years, allowing no inferences for long-term use or long-term effects. Specifically, no study had sufficient follow-up and sample size to investigate effects in long-term users. Furthermore, the investigation of long-term effects on manifestation of cardiac disease in later adulthood, perhaps decades after stimulant treatment, will need to wait until the first large cohorts of ADHD children from the 1990s have reached later stages of adulthood.

As all available evidence is based on retrospective analysis of healthcare utilization data, two major concerns for bias exist. First, stimulants might be channelled toward healthier children resulting in inflated incidence rates in the non-users and masking adverse stimulant effects. Florida-II shows a

comprehensive comparison of baseline characteristics that indeed suggest slightly healthier users when compared to non-users. However, the observed differences were subtle and do not suggest presence of residual confounding after propensity score adjustment. Second, measurement bias, including limited sensitivity or specificity in endpoint ascertainment could result in underestimated stimulant effects. However, the severity of events suggests that a large portion will result in healthcare utilization, and thus comprehensive capture with claims data, and limited miscoding. This notion was confirmed by the Vanderbilt chart review results after sudden cardiac death cases that were secondarily attributed to trauma were removed from the analysis. For these reasons, residual bias, if any, is expected to be subtle.

Conclusion

Studies concur that serious cardiac events in healthy children are extremely rare and not associated with central nervous system stimulants used in care of children with ADHD. With an estimated incidence rate of less than three serious cardiovascular events per 100,000 patient-years of stimulant use, limited chance for bias across studies, and an upper confidence interval limit of 40 % in the Florida-II study, adverse cardiac events of stimulants are expected to affect a very small number of children. Of note, the findings may not generalize to children who use stimulants over many years or long-term effects of stimulants that may manifest in later adulthood.

Compliance with Ethics Guidelines

Conflict of Interest Almut G. Winterstein has received research funding for stimulant safety studies from the Agency for Healthcare Research and Quality (AHRQ) and the Florida Agency for Health Care Administration/Medicaid. She was invited to present respective findings at the World ADHD Conference 2013 in Milan and received travel support from the organizers of the conference.

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

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