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Cardiac Safety of Methylphenidate Versus Amphetamine Salts in the Treatment of ADHD

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Abstract

OBJECTIVES—Safety concerns about central nervous system stimulants for the treatment of attention-deficit/hyperactivity disorder (ADHD) include adverse cardiac effects. This study aimed to compare the risk for cardiac events in users of methylphenidate and amphetamine salts.

METHODS—A retrospective cohort design using claims data from the Florida Medicaid fee-for-service program representing a total of 2 131 953 children and adolescents was used. The analysis included all beneficiaries who were between 3 and 20 years of age, enrolled between July 1994 and June 2004, had at least 1 physician diagnosis of ADHD and were newly started on methylphenidate or amphetamine salts. Each month of follow-up was classified according to stimulant use into current use or former use. We defined cardiac events as first emergency department (ED) visit for cardiac disease or symptoms. Risk between current users of methylphenidate versus amphetamine salts and former users of drugs in these categories was compared by using a time-dependent Cox proportional hazard model that adjusted for differences in gender; race; age; year of the index date; disability; congenital anomalies; history of circulatory disease; history of hospital admission; and use of antidepressants, antipsychotics, and bronchodilators.

RESULTS—A total of 456 youth visited the ED for cardiac reasons during 52 783 years of follow-up. After adjustment for differences in covariates, the risk for cardiac ED visits was similar among current users of methylphenidate or amphetamines. Periods of former use had a similar risk between youth with an exposure history to methylphenidate or amphetamine.

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CONCLUSION—Exposure to methylphenidate and amphetamines salts showed similar risk for cardiac ED visits. Additional population-based studies that address manifestation of serious heart disease, especially after long-term use, dosage comparisons, and interactions with preexisting cardiac risk factors are needed to inform psychiatric treatment decisions.

Keywords

central nervous system stimulants; methylphenidate; amphetamine; safety; cardiac events; psychopharmacology; attention-deficit/hyperactivity disorder; child and adolescent mental health; pharmacoepidemiology

Although the evidence base for the cardiac effects of central nervous system stimulants (stimulants) that are used for the treatment of attention-deficit/hyperactivity disorder (ADHD) is still unsatisfactory, concerns have resulted in a Food and Drug Administration (FDA) mandate for medication guides to alert patients to potential cardiovascular risks and adverse psychiatric symptoms.[1] Evidence for cardiac adverse effects consists of clinical trial data[2–5] that demonstrate increases in heart rate (~5 beats per minute) and blood pressure (~2 to 7 mm Hg measured as diastolic or systolic and diastolic pressure) and case reports of cardiac sudden death and other severe cardiac adverse effects in children who are exposed to stimulants. In addition, we recently published the first population-based cohort study of >50 000 children with ADHD, which reported a 20% increased risk for emergency department (ED) visits for cardiac symptoms for all stimulants combined.[6]

Few data regarding the comparative safety profile of the individual stimulant agents are available. A recent systematic review of randomized clinical trials conducted by the Centre for Review and Dissemination at the University of York on behalf of the British National Institute for Health and Clinical Excellence (NICE) concluded that head-to-head comparisons of stimulants or atomoxetine are scarce and that adequate and informative data on adverse effects are generally lacking.[7] The Canadian regulatory agency decided selectively to withdraw approval for Adderall (Shire US Inc, Florence, KY), an amphetamine salt, in 2005—a decision that was revoked 6 months later—on the basis of case reports collected by the World Health Organization and FDA adverse drug reaction reporting programs. The FDA review of spontaneous reports between 1999 and 2003 revealed calculated reporting rate ratios for amphetamine versus methylphenidate >1 in all categories of events, ranging from 2.3 to 7.6.[8] No large population-based study has evaluated the comparative risk.

Information on the comparative safety of the 2 most prevalent substances that are used to treat ADHD would aid in the assessment of the risk/benefit of pharmacologic treatment and inform treatment decisions. This study aimed to compare the risk for adverse cardiac events in users of methylphenidate and amphetamine salts.

METHODS

This was a retrospective cohort study that used data assembled from the Florida Medicaid fee-for-service program, which represented a total of 2 131 953 children and adolescents during the 10-year study period. Details on patient characteristics and drug use pattern have been reported elsewhere.[9] We included all beneficiaries who were between 3 and 20 years of age, enrolled between July 1994 and June 2004, and had at least 1 inpatient or outpatient claim for ADHD, defined as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 314.xx. A new-user design wherein patients entered the cohort when they were newly started on methylphenidate or amphetamine salts (index date) was used.[10] The index date had to be preceded by a 6-month period of continuous

eligibility without any claim for methylphenidate or amphetamine. Patients with claims for atomoxetine (n = 3702), methamphetamine (n = 979), or pemoline (n = 1123) at any time during the study period were excluded. Patients were followed until the outcome of interest occurred, eligibility ended, a diagnosis for malignant neoplasm occurred, they turned 21 years of age, switched from 1 drug class to the other, or started to use drugs from both categories concomitantly, whichever came first. Thus, only the initial treatment period with the second of the 2 ADHD drug categories was considered in an attempt to avoid bias when patients were switched to 1 drug category because the first category was not tolerated.

Use of central nervous system stimulants was determined from prescription drug claims for methylphenidate, amphetamine, and dexamphetamine, including all immediate- and sustained-release forms. Because prescriptions are typically filled for a 30-day supply, we assumed that each prescription was active during the month it occurred and the subsequent month. For each cohort member, each month of follow-up was classified according to stimulant use into 2 categories: (1) time when a stimulant prescription was active was assigned to the current use period; and (2) time after any month of current use with no active claim was classified as former use. The category former use was established because, within each drug cohort, the individual characteristics of this group should be similar to those of current use. Thus, the risk for cardiac events between former use periods of methylphenidate and amphetamine salts should be similar if the selection of a specific stimulant was not driven by patient cardiac risk factors (confounding by indication).

Consistent with our previous report, we defined cardiac events as all ED visits with the principal diagnosis for the following diseases or symptoms: acute myocardial infarction (ICD-9-CM 410.xx, 411.8x), stroke (430.xx–436.xx), hypertensive disease (401.xx–405.xx, excluding malignant causes 40x.0), angina (413.xx), aortic or thoracic aneurysm (441.0x, 441.1x), arrhythmias (426.89, 427.xx), syncope (780.2x), or tachycardia or palpitation (785.0x, 785.1x).

Patients with congenital anomalies of the heart and other hereditary diseases that are often associated with cardiac adverse events were identified by presence of an inpatient or outpatient claim at any time in the study period for the following conditions: hereditary hemolytic anemia (ICD-9-CM 282.xx), hemophilia (286.0x–286.4x), anomalies of bulbus cordis and cardiac septal closure (745.xx), other congenital anomalies of heart (746.xx), congenital anomalies of circulatory system (747.0–747.4xx), Down syndrome (758.0x), gonadal dysgenesis (758.6x), and fragile × syndrome (759.83). Preexisting heart problems was defined as presence of any inpatient or outpatient claim within 6 months before the index date for diseases of the circulatory system (390.xx–459.xx), syncope (780.2x), tachycardia or palpitation (785.0x, 785.1x), and chest pain (786.50). Using the same prediagnosis/pretreatment time period, we used 2 variables as proxy for general health status, namely hospital admission for any cause and whether Medicaid eligibility was based on disability (designated by Medicaid as “SSI” = Supplemental Security Income). To account for concurrent use of other drugs that have been associated with cardiac effects, we ascertained drug claims data for appetite suppressant drugs, monoamineoxidase inhibitors, bronchodilators (β-agonists, ipatropium bromide, or theophylline analogs), antidepressants, and antipsychotics. No attempt was made to find claims for oral decongestants because most were available over-the-counter and an attempt to account for their use on the basis of claims data would be prone to misclassification.

Beneficiaries with conflicting information on self-reported race/ethnicity, gender, and age were assigned the respective category that was most often used in the Medicaid database. For race/ethnicity, specific designation of a race was given priority over the category “other.” Age was categorized according to population-based distributions of mortality and

morbidity statistics into <5, 5 to 9, 10 to 14, and ≥15 years. Last, because drug use patterns were expected to shift during the 10-year study period, the year of the index date was included as covariate as well.

Risk between current users of methylphenidate versus amphetamine salts (mixed amphetamine salts or dexamphetamine) and former users of drugs in these categories was compared using a time-dependent Cox proportional hazard model to adjust for group differences in age; gender; race; year of the index date; SSI; congenital anomalies; history of circulatory disease; history of hospital admission; and use of antidepressants, antipsychotics, and bronchodilators as covariates. Three binary independent variables above versus below age thresholds of 5, 10, and 15 years were used. Likewise, 3 independent variables for race/ethnicity—white versus nonwhite, black versus nonblack, and Hispanic versus non-Hispanic—were used. Age and use of antidepressant, antipsychotic, and asthma drugs were assessed for every month of follow-up and included in the regression model as time-dependent variables. All variables were entered in a stepwise forward manner and included when they showed an independent significant association with the clinical end point as dependent variable ($P < .05$). Data management and analysis were conducted with SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

The final cohort consisted of 30 576 youth who had a qualifying new diagnosis of ADHD and were newly started on methylphenidate or amphetamine salts (Table 1). 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. The percentage of patients who contributed at least 6 months of observation on stimulants was similar: 52.6% of all amphetamine users and 54.5% of methylphenidate users. Noteworthy differences between the 2 cohorts included a larger propensity for concomitant use of antidepressants in current and former amphetamine users and a slightly larger representation of amphetamine users in more recent study years, reflecting the shorter availability of immediate- and sustained-release amphetamines. The distribution of patients with a history of circulatory disease, disability, and history of hospitalization was similar between the groups.

A total of 456 youths visited the emergency department (ED) for cardiac reasons during a total number of 52 783 years of follow-up (Table 2). After adjusting for covariates the risk for ED visits was similar among methylphenidate and amphetamine users, with an adjusted hazard ratio of 1.01 (95% confidence interval 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, 95% CI 0.73–1.25).

Variables that showed a positive association with ED visits in both models (comparison of current use and comparison of former use) were use of bronchodilators (for the current use comparison: HR = 1.88, 95% CI 1.40–2.53), use of antidepressants (HR = 1.67, 95% CI 1.29–2.15), use of antipsychotics (HR = 1.90, 95% CI 1.43–2.53), age 15 years and older (HR = 1.65, 95% CI 1.26–2.16), congenital anomalies (HR = 3.12, 95% CI 2.22–4.38), and history of circulatory disease or cardiac symptoms (HR = 2.72, 95% 1.85–4.01). Switching patterns that might indicate intolerability of a specific drug were also similar between groups. A total of 4890 or 26.8% of youths who were started on methylphenidate switched during the study period to amphetamine; and 2947 or 23.9% initial amphetamine users were switched to methylphenidate.

DISCUSSION

Concerns that amphetamines might have a larger propensity to cause cardiac adverse events could not be confirmed in this study. Both unadjusted and adjusted relative risk estimates did not support a pronounced risk difference between the 2 drug classes. Moreover, use and switching pattern did not suggest that a certain drug class was avoided because of cardiac or other adverse effects. Although the 2 drug classes combined did show an increased risk for cardiac ED visits when compared with nonusers of stimulants in our previous research in the same population,[6] the type of stimulant as evaluated in this study did not seem to affect the incidence of cardiac problems. It should be noted in this context that our previous study was not powered to evaluate the risk for manifestation of heart disease as indicated, for example, by hospitalizations for arrhythmia, myocardial infarction, or sudden cardiac death. Likewise, this study is confined to cardiac symptoms and inferences about the comparative risk for serious cardiac events of the 2 stimulant classes cannot be made.

Analyses of spontaneous reports have suggested a slightly higher risk for amphetamines than methylphenidate,[8] but such comparisons are prone to reporting bias and ought to be validated with controlled studies. Our literature review identified only 2 head-to-head trials that formally compared adverse effect rates between the 2 drug classes. One study, which randomly varied daily exposure to amphetamine salts, methylphenidate, and placebo in school children, reported a greater frequency of appetite loss and trouble sleeping in children who received amphetamine.[11,12] Similar findings were reported in a crossover trial, which found an increase in the severity of appetite loss and insomnia along with development of some negative emotional symptoms during exposure to dexamphetamine when compared with methylphenidate.[13] Both studies followed a small sample of patients during a short period and may have lacked the ability to detect differences in manifestation of cardiac symptoms or heart disease. The only population-based long-term study, which followed children of the 1976–1982 Rochester, MN, birth cohort, found a higher overall adverse effect rate during episodes of amphetamine treatment when compared with methylphenidate.[14] Comparisons did not detail the type of adverse effects. Thus, no published literature that offers comparative data on the cardiac adverse effect potential of methylphenidate versus amphetamine is available.

This is the first study to report comparative safety data of stimulants in a cohort of >30 000 children and adolescents. Its strengths, besides its large sample size, include several methodologic features that deserve additional discussion. First, ED visits were chosen as clinical end point because they occur more frequently than hospital admissions or cardiac death and provided the best power to detect even subtle difference between drugs. Detectable hazard ratios at $P = .05$ (2-sided) with 80% power to detect a difference between methylphenidate and amphetamine cohorts, given the number of events and distribution of times at risk to each treatment, were as follows: current users 1.44; former users 1.58; overall 1.33.

One might argue that ED visits vary in acuity and may reflect parent concern rather than manifestation of acute cardiac adverse effects; however, although some events may not have been of the clinical magnitude to warrant a visit to the ED, the comparison of event rates between drug categories remains valid as long as parent concern did not vary by type of drug. Both drug classes include similar warnings about cardiac adverse effects and should influence parent and patient behavior to a similar extent. Concerns of cardiac adverse effects may have increased since the Canadian authorities announced the withdrawal of Adderall, which occurred, however, after the period considered in this analysis.

Second, because psychiatric treatment bases drug selection and dosage often closely on patient response, it is conceivable that medications were switched or discontinued not only when the desired psychiatric effect was not achieved but also when early cardiac signs and symptoms manifested. We limited our comparisons to new stimulant users in an attempt to avoid biased comparison groups in which high-risk patients had been switched systematically to 1 drug category because the other was not tolerated. For the same reason, patients were censored when switching occurred. Thus, the results presented here reflect the original response of previously stimulant-naive patients. Additionally supportive of the argument that initial drug choice did not seem to be associated with cardiac adverse effects is the observation that similar proportions of patients switched from 1 drug category to the other, as well as the similar duration for which youth were exposed to the respective stimulant categories. Switching is, of course, also influenced by drug effectiveness, and differences or similarities in duration of use may reflect the total risk/benefit profile of the studied drug classes.

Third, observational studies are compromised by the inability to address unmeasured confounders and, thus, cannot establish causality. Our multivariate analysis showed that we successfully adjusted for selected cardiac risk factors, but other confounders may have been missed. This may include concomitant use of other medications with cardiac adverse effects that were not reimbursed by Medicaid, such as oral decongestants, anorexigenic drugs and recreational drugs, or presence of congenital heart disease not reflected in the claims. The comparison of former use periods is important in this context. Under the assumption that the potential risk for cardiac adverse effects is reversible when exposure is discontinued, former users of methylphenidate and amphetamines should have similar risk when the original drug selection was not affected by cardiac risk factors. The similar ED visit rates during former use periods suggest that the comparison groups were similar and that significant confounding factors were likely addressed with the multivariate model.

Last, reliance on claims data is prone to misclassification (ie, mistakes in the determination of drug exposure, confounding variables, and outcomes). Periods of exposure may have been misclassified when patients interrupted treatment and extended a month’s supply over longer periods. This would result in an underestimation of the rate of adverse effects and, thus, decrease the ability to detect differences between drugs; however, given our focus on the initial treatment period and the rigorous censoring criteria, it is questionable whether misclassification could be severe enough to result in hazard ratios so close to 1 as observed in this study.

Several questions related to the comparative safety profile remain unanswered. First, our study period did not allow a comparison of stimulants and atomoxetine because the latter was approved only in 2002. Atomoxetine is not categorized as a central nervous system stimulant, and it is unclear whether it offers a safer alternative. Second, this analysis evaluated the effect of stimulants on cardiac symptoms and did not have sufficient sample size to address manifestation of heart disease or severe cardiac events such as myocardial infarction or cardiac death. Third, drug dosing was not considered in this report because treatment recommendations include careful titration of dosages according to patient response and occurrence of adverse effects. Thus, dosages were expected to vary and, in many instances, to reflect risk/benefit considerations. Comparative dosage studies that weigh psychotropic effectiveness against potential cardiac adverse effects would be valuable in guiding treatment decisions.

CONCLUSIONS

Exposure to methylphenidate and amphetamine salts showed similar risk for ED visits for cardiac reasons. Additional population-based studies that address manifestation of serious heart disease, especially after long-term exposure, dosage comparisons, and effects of other cardiac risk factors are needed to inform psychiatric treatment decisions further.

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ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
FDA	Food and Drug Administration
ED	emergency department
ICD-9-CM	*International Classification of Diseases*, Ninth Revision, Clinical Modification
SSI	Supplemental Security Income

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WHAT'S KNOWN ON THIS SUBJECT

Analyses of spontaneous reports of adverse drug reactions to the FDA suggested a slightly higher risk for amphetamines than methylphenidate, but comparisons are prone to reporting bias.

WHAT THIS STUDY ADDS

This is the first large population-based study to describe the comparative risk of methylphenidate and amphetamine salts in the treatment of ADHD.

TABLE 1

Characteristics of Amphetamine and Methylphenidate Users

Characteristic	Amphetamine Users (*N* = 12 338)		Methylphenidate Users (*N* = 18 238)	
	Current	Former	Current	Former
Age at first assignment to group, y, average ± SD	8.3±3.2	9.1±3.3	8.5±2.9	9.2±3.0
Male, %	71.3		73.1	
Race/ethnicity, %				
White	51.4	46.7	48.2	44.0
Black	27.9	30.8	31.6	34.7
Hispanic	14.8	16.0	14.4	15.3
Use of bronchodilators, %	17.0	15.5	16.3	15.5
Concomitant use of				
Antidepressants, %	20.9	16.4	16.4	14.0
Antipsychotics, %	12.7	11.6	8.2	8.2
Entered cohort (average of study months July 1994 to June 2004)	March 2001		May 1999	
Follow-up time, mo, average ± SD	19.2±18.8		22.5±23.8	
Eligible as aid to disabled, %	23.7		23.1	
Circulatory disease				
Congenital anomalies, %	1.6		1.7	
History of circulatory disease/symptoms, %	2.0		1.8	
Previous hospital admission for any cause, %	3.1		2.8	

TABLE 2

ED Visits for Cardiac Causes Among Current and Former Users of Methylphenidate and Amphetamines

Parameter	Person-years	Youth With ED Visits	Crude Rate (ED Visits Per 1000 Patient-years)	RR Unadjusted (95% CI)	HR Adjusted (95% CI)
Current use					
Methylphenidate	17 175	171	10.0	1.00	1.00
Amphetamine	11 110	105	9.5	0.95 (0.74–1.21)	1.01 (0.80–1.28)
Former use					
Methylphenidate	15 795	114	7.2	1.00	1.00
Amphetamine	8704	66	7.6	1.05 (0.78–1.42)	0.95 (0.73–1.25)