ORIGINAL ARTICLE

ADHD Drugs and Serious Cardiovascular Events in Children and Young Adults

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ABSTRACT

BACKGROUND

Adverse-event reports from North America have raised concern that the use of drugs for attention deficit–hyperactivity disorder (ADHD) increases the risk of serious cardiovascular events.

METHODS

We conducted a retrospective cohort study with automated data from four health plans (Tennessee Medicaid, Washington State Medicaid, Kaiser Permanente California, and OptumInsight Epidemiology), with 1,200,438 children and young adults between the ages of 2 and 24 years and 2,579,104 person-years of follow-up, including 373,667 person-years of current use of ADHD drugs. We identified serious cardiovascular events (sudden cardiac death, acute myocardial infarction, and stroke) from health-plan data and vital records, with end points validated by medical-record review. We estimated the relative risk of end points among current users, as compared with nonusers, with hazard ratios from Cox regression models.

RESULTS

Cohort members had 81 serious cardiovascular events (3.1 per 100,000 person-years). Current users of ADHD drugs were not at increased risk for serious cardiovascular events (adjusted hazard ratio, 0.75; 95% confidence interval [CI], 0.31 to 1.85). Risk was not increased for any of the individual end points, or for current users as compared with former users (adjusted hazard ratio, 0.70; 95% CI, 0.29 to 1.72). Alternative analyses addressing several study assumptions also showed no significant association between the use of an ADHD drug and the risk of a study end point.

CONCLUSIONS

This large study showed no evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular events, although the upper limit of the 95% confidence interval indicated that a doubling of the risk could not be ruled out. However, the absolute magnitude of such an increased risk would be low. (Funded by the Agency for Healthcare Research and Quality and the Food and Drug Administration.)

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Medications that are used to treat attention deficit–hyperactivity disorder (ADHD) are prescribed for more than 2.7 million children in the United States each year[1] and have been considered to be relatively safe.[2-5] However, reports of adverse events from Canada and the United States that have included cases of sudden death, myocardial infarction, and stroke in conjunction with the use of these drugs have raised concern about their safety.[6,7] Although case reports from adverse-event reporting systems can be an important source for identifying medication safety signals, they cannot reliably quantify risk. Thus, there is a compelling need to obtain better safety data for these drugs. We used data from four large, geographically and demographically diverse U.S. health plans to conduct a retrospective cohort study of the use of ADHD drugs and the risk of serious cardiovascular events in children and young adults, with review of medical records to validate study end points. The study was conducted in parallel with a study of ADHD drug use and serious cardiovascular events in adults between the ages of 25 and 64 years.

Methods

Data Sources

We obtained study data from computerized health records of four health plans that together annually covered 22.4 million persons during the study period: Tennessee Medicaid, Washington State Medicaid, Kaiser Permanente California (Northern and Southern regions), and OptumInsight Epidemiology (national private insurance health-plan data). We augmented health-plan data with linkage to state death certificates and the National Death Index. Health-plan data included enrollment records, outpatient and inpatient claims, and records of filled prescriptions (including the dispensing date, drug name, dose, quantity, and duration of supply), which have been shown to be good measures of medication use.[8-11] The initiation of the study differed according to site on the basis of the earliest availability of the site's computerized data (ranging from 1986 to 2002). Follow-up concluded for all sites at the end of 2005. Each site prepared standardized files from health-plan data and used computer programs from the lead site (Vanderbilt University) to define study variables and create files in which identifiers of patients had been removed. These files were sent to the lead site for analyses.

Study Population

To assemble the cohort, we identified patients who met the following criteria: use of an ADHD drug (methylphenidate, dexmethylphenidate, dextroamphetamines, amphetamine salts, atomoxetine, or pemoline) during the study period; an age of 2 to 24 years on the first day of qualifying use; continuous enrollment with drug benefits for 365 days preceding the first day of qualifying use (allowing for short administrative gaps in enrollment); and the absence of possibly life-threatening serious illness (Section 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Because patients with congenital heart disease may be vulnerable to the effects of ADHD medications, such patients were included in the study. Exclusion criteria included a hospital discharge during the preceding 365 days with a primary diagnosis of acute myocardial infarction or stroke. The last day of study follow-up was the last day of the study or the date on which the patient no longer met study criteria. A given patient was allowed to reenter the cohort as long as all the cohort eligibility requirements were met.

For each patient receiving an ADHD medication, we randomly selected up to two nonuser control subjects from health-plan members at the same site who were enrolled on the first day of qualifying use at the age of 2 to 24 years, who met continuous-enrollment requirements, and who did not have a serious illness. Nonusers were matched with users on the basis of calendar year, age, and sex and were allowed to have previous nonqualifying use of ADHD drugs before the first day of qualifying use. Follow-up for nonusers began on the first day of qualifying use for the matched users of ADHD drugs and ended on the nonuser's last day of study follow-up (Section 2 in the Supplementary Appendix). Follow-up time did not include the time during hospitalization and the 30 days after discharge because in-hospital deaths were not considered to be study end points and health-plan files did not include drugs dispensed in the hospital.

Use of Study Drugs

Every person-day during study follow-up was classified according to use of ADHD drugs (Section 2 in the Supplementary Appendix). Current use

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was defined as use during the period between the prescription start date and the end of the days of supply (including up to a 7-day carryover from previous prescriptions). Former use was defined as use during the period after current use through the end of study follow-up. Nonuse was defined as no prescribed use of ADHD drugs on the day being classified or any preceding days. Former users and nonusers could become current users of ADHD drugs during follow-up, and when this occurred, their user person-time was classified as described above.

STUDY END POINTS

The primary study end point was a serious cardiovascular event, which was defined as sudden cardiac death, myocardial infarction, or stroke. Sudden cardiac death was defined as a sudden, pulseless condition or collapse consistent with a ventricular tachyarrhythmia occurring in a community setting and including both fatal and resuscitated cardiac arrest (cases in which an arrest occurred in the community but the patient was successfully resuscitated).[12-16] The diagnosis of acute myocardial infarction required hospitalization and met the international diagnostic criteria for myocardial infarction.[17-19] Stroke was defined as an acute neurologic deficit of sudden onset that persisted for more than 24 hours, corresponded to a vascular territory, and was not explained by other causes (e.g., trauma, infection, vasculitis, or profound systemic hypotension).[17,20,21]

Potential end points were identified from claims and vital records and adjudicated through review of all pertinent medical records, including hospitalizations, reports of emergency medical services, autopsies, and death certificates (Section 3 in the Supplementary Appendix). Criteria for potential cases were intentionally broad to increase sensitivity because we anticipated that study end points would be rare and planned to review medical records for all potential cases. All events were adjudicated by two cardiologists (for sudden cardiac death and acute myocardial infarction) or two neurologists (for stroke). These adjudicators reviewed cases from all sites and were unaware of exposure status (Section 4 in the Supplementary Appendix). Disagreements among adjudicators (<5% of cases) were resolved by consensus with the study principal investigator.

Cases were excluded if the documentation suggested a cause other than a cardiovascular cause (e.g., motor-vehicle accident or drug overdose) or for sudden cardiac death, if clinically severe heart disease was present and sudden cardiac death was not unexpected (e.g., end-stage congestive heart failure). Congenital heart defects that had not been diagnosed until autopsy were noted but did not result in the exclusion of the potential case. In cases in which we were unable to obtain pertinent medical records or had insufficient information for adjudication (21% of cases), we determined the case status using a computer case definition, derived from cases with completed adjudication. The positive predictive value of the computerized case definition for serious cardiovascular events was 91% (Section 5 in the Supplementary Appendix).

STUDY OVERSIGHT

The study was approved by the institutional review board at each of the participating institutions and by the Food and Drug Administration (FDA) Research in Human Subjects Committee. In addition, permission was obtained from the data sources for each site. In all cases the need for informed consent was waived. The study was planned by the authors. Data were gathered from each site and analyzed by the study biostatistician, who vouches for the data and the analysis along with the first author.

STATISTICAL ANALYSIS

We calculated the hazard ratio for users of ADHD drugs, as compared with nonusers, using Cox regression models with robust sandwich variance estimators to account for the matched study design and for persons entering the cohort multiple times.[22] The hazard ratio was adjusted for both baseline characteristics and changes in characteristics that occurred during follow-up. We calculated the adjusted incidence of end points by multiplying the incidence rate in the nonusers by the hazard ratio.

Because the number of covariates that reflected baseline cohort characteristics was large in comparison to the number of end points, we adjusted for these covariates by including a site-specific propensity score in the regression models. The propensity score was defined as the probability that the patient was currently receiving an ADHD drug on the first day of study follow-up, estimated for each site by means of logistic regression.[23] The baseline variables in

Table 1. Study Cohorts, According to Site.

Variable	Tennessee Medicaid	Kaiser Permanente California*	OptumInsight Epidemiology	Washington Medicaid	Total
Study period	1986–2005	1999–2005	1998–2005	2000–2005	1986–2005
Number in cohort	200,198	191,772	692,187	116,281	1,200,438
Percent of patients enrolled in Medicaid	100.0	4.4	0	100.0	27.0
Mean age of patients (yr)	8.7	11.1	12.0	10.0	11.1
Mean year of study entry	1999	2002	2002	2002	2002
Mean duration of follow-up (yr)	3.9	2.6	1.5	2.1	2.1

* This category includes Kaiser Permanente Northern and Southern California regions.

the propensity score included sociodemographic characteristics as well as information on medical care encounters consistent with psychiatric disorders, asthma and other respiratory illnesses, seizure and other neurologic disorders, unintentional injuries, cardiovascular diseases, and other diseases. For each site, we tested the adequacy of the propensity-score models by calculating the propensity-score adjusted means of baseline variables for users and nonusers of ADHD drugs; these values were similar (Section 6 in the Supplementary Appendix).

In our primary analysis, we adjusted for study site, propensity-score decile, and several time-dependent covariates (medical and psychiatric conditions, health care utilization, age, and calendar year) (Section 7 in the Supplementary Appendix). In order to test key study assumptions, we performed additional analyses that were stratified according to age group (2 to 17 years and 18 to 24 years) and that used alternative exposure groups, cohort inclusion criteria, and end-point exclusions. We performed all statistical analyses using SAS software, version 9.1 (SAS Institute).

RESULTS

STUDY POPULATION

The study cohort included 1,200,438 children and young adults. The mean age of cohort members at baseline was 11.1 years (mean range at the study sites, 8.7 to 12.0) (Table 1). The mean length of follow-up for the cohort was 2.1 years (mean range at the study sites, 1.5 to 3.9) for a total follow-up of 2,579,104 person-years. The characteristics of current users and nonusers at baseline are shown in Table 2. Generally, current users had more evidence of health care utilization of all types. In addition, they had greater prevalence of psychiatric illnesses and greater use of psychotropic medications. Current users were also more likely to have asthma, seizures, and congenital heart defects. For both current users and nonusers, alcohol and drug use, as determined from records of medical care encounters, were uncommon.

STUDY END POINTS

A total of 81 cohort members had a serious cardiovascular event, or 3.1 per 100,000 person-years, including 33 sudden cardiac deaths (1.3 per 100,000 person-years), 9 acute myocardial infarctions (0.3 per 100,000 person-years), and 39 strokes (1.5 per 100,000 person-years). Characteristics of the confirmed cases according to exposure to an ADHD drug are shown in Section 8 in the Supplementary Appendix. In the multivariate model, an older age, current use of an antipsychotic drug, a major psychiatric illness, a serious cardiovascular condition, and chronic illness were associated with an increased risk of serious cardiovascular events (Section 7 in the Supplementary Appendix).

There were 7 confirmed events among 373,667 person-years of follow-up for current users, 25 confirmed events among 607,475 person-years of follow-up for former users, and 49 confirmed events among 1,597,962 person-years of follow-up for nonusers. As compared with the nonusers, the adjusted rate of serious cardiovascular events did not differ significantly among current users of ADHD drugs (hazard ratio, 0.75; 95% confidence interval [CI], 0.31 to 1.85) or among former users (hazard ratio, 1.03; 95% CI, 0.57 to 1.89) (Fig. 1). When former users served

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as the reference group (in which the possible effect of unmeasured confounding was assessed), there was no increased risk of serious cardiovascular events among current users (hazard ratio, 0.70; 95% CI, 0.29 to 1.72) (Section 9 in the Supplementary Appendix). There was also no evidence of increased risk for the individual end points of sudden cardiac death, acute myocardial infarction, or stroke (Table 3). We found no evidence of increased risk for methylphenidate (hazard ratio, 0.96; 95% CI, 0.31 to 2.97), the most frequently used ADHD drug (Section 10 in the Supplementary Appendix). Data were too sparse for other individual drugs to fit regression models.

ALTERNATIVE ANALYSES

We performed several alternative analyses to test the robustness of study findings (Table 4, and Section 11 in the Supplementary Appendix). To assess for possible bias from the inclusion of persons who used ADHD drugs before the beginning of follow-up,[10] we restricted current users of ADHD drugs only to new users (which was defined as no use of ADHD drugs during the 365 days preceding the first day of qualifying use). Findings were essentially identical to those of the primary analysis (hazard ratio, 0.73; 95% CI, 0.24 to 2.10). When we included seven patients who had been excluded from the primary analysis because they had evidence of severe underlying cardiac disease for which sudden cardiac death would not be unexpected, we found no increased risk for current users (hazard ratio, 0.71; 95% CI, 0.29 to 1.72). In analyses that included only children 2 to 17 years of age, we found no association between the use of ADHD drugs and serious cardiovascular events (hazard ratio, 0.98; 95% CI, 0.41 to 2.36). When children with evidence of serious psychiatric disease were excluded, we also found no significant association (hazard ratio, 0.66; 95% CI, 0.20 to 2.16).

We also performed analyses to test other key study assumptions. A site-specific analysis suggested a potential difference between Medicaid and non-Medicaid sites, although numbers were very small and we saw no evidence of significant heterogeneity in pooled analyses of rate differences between users and nonusers (Section 12 in the Supplementary Appendix). Another analysis expanded the definition of current use to include the 89 days after the end of current use to account for a possible misclassification in exposure related to the clinical use of ADHD drugs

Table 2. Characteristics of Cohort Members, According to the Use of ADHD Drugs at Baseline.*

Variable	Nonuser	Current User
Demographic characteristic		
Mean age (yr)	11.1	11.1
Male sex (%)	70.9	71.1
Nonwhite race (%)†	50.5	36.8
Residence in metropolitan area (%)	78.4	77.1
Psychiatric condition (%)		
ADHD diagnosis	1.3	57.4
Major depression	1.6	10.4
Bipolar disorder	0.2	2.1
Psychosis	0.1	0.5
Autism	0.2	1.4
Mental retardation	0.6	4.0
Previous suicide attempt	0.1	0.3
Use of psychotropic medication (%)		
Antidepressant	1.8	15.0
Mood stabilizer	0.5	4.2
Antipsychotic drug	0.4	5.2
Benzodiazepine	0.1	0.5
Medical condition (%)		
Asthma	16.1	22.1
Seizures	0.6	2.1
Obesity	0.9	1.2
Congenital heart defect‡		
Major	0.5	0.8
Minor	3.6	6.9
Diabetes	0.4	0.5
Other serious health condition§	0.9	1.3
Substance use (%)		
Alcohol or drugs	0.4	1.5
Smoking	0.6	0.9
Use of health services (%)		
Psychiatric hospitalization	0.3	1.9
Medical hospitalization	2.5	4.1
Medical emergency department visit	12.9	15.8
Any psychiatric care	5.4	63.1
Any cardiovascular care	4.0	6.0
Any outpatient visit	75.1	92.9
Any prescription use	22.0	31.7

* All analyses have been adjusted for age, sex, and study site. All data were obtained from claims and include medications used in the 365 days before study entry. P<0.001 for all between-group comparisons except for age and sex.

† Race was reported by individual health plans, whose data-collection procedures varied.

‡ Major congenital heart defects included common truncus, transposition of the great vessels, tetralogy of Fallot, common ventricle, endocardial cushion defect, pulmonary atresia, tricuspid atresia, hypoplastic left heart syndrome, coarctation of the aorta, and total anomalous pulmonary venous return. Minor congenital heart defects included any other congenital heart anomaly.

§ Other serious health conditions included pneumonia, thyroid disease, and kidney disease.

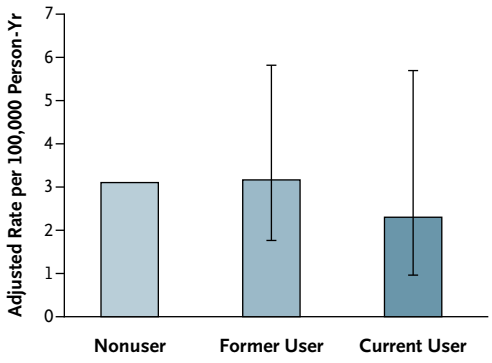

Figure 1. Adjusted Rates of Serious Cardiovascular Events, According to the Use of ADHD Drugs.

Rates per 100,000 person-years were adjusted by multiplying the rate in the reference group (nonusers) by the hazard ratios for former and current users. Hazard ratios were estimated with the use of Cox regression models, which were adjusted for the site-specific propensity-score decile, study site, medical conditions (serious cardiovascular disease and serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general access to medical care), age, and calendar year. The I bars indicate 95% confidence intervals.

or for drugs that were discontinued after prodromal symptoms of an end point (e.g., headache preceding stroke). Finally, we performed an analysis in which time-dependent variables were fixed at baseline. The findings of these analyses were essentially identical to those reported here.

DISCUSSION

Several regulatory and policy decisions resulted from the review of adverse-event reports of serious cardiovascular events associated with the use of ADHD drugs in Canada and the United States. In Canada, Health Canada removed and then reinstated marketing of extended-release mixed amphetamine salts.[6,7] In the United States, three different FDA advisory committees considered the issue and recommended a black-box warning for stimulants, as well as a medication guide for patients.[24] In a controversial policy statement, the American Heart Association stated that obtaining electrocardiograms in children who were initiating ADHD stimulant therapy was "reasonable,"[25] a recommendation that was subsequently revised on the basis of input from several pediatric organizations.[24] This led to concern and confusion among health care providers, patients, and families about the risks of these drugs.[26] In this context, we studied the cardiovascular safety of ADHD drugs in more than 1.2 million children and young adults from four geographically diverse health plans with more than 2.5 million person-years of follow-up. The point estimate of the relative risk provided no evidence that the use of ADHD drugs increased the risk of serious cardiovascular events, although the upper limit of the 95% confidence interval was consistent with up to a doubling in the risk.

In the study population, which excluded children with possibly life-threatening illness, the incidence of serious cardiovascular events was 3.1 per 100,000 person-years, a finding that was consistent with other studies.[27-30] The low number of events limited the statistical power of the study, particularly for individual end points and individual drugs, as well as for subgroups that might be particularly vulnerable to the effects of ADHD drugs. We also had limited information for longer durations of use.

Could the study findings be the result of confounding? The comparison between current users and nonusers at baseline indicated a greater incidence of medical and psychiatric coexisting conditions among current users. The analyses were adjusted for an extensive set of cardiovascular disease variables, which were included in site-specific propensity scores. Using this method, we could account for many important risk factors for cardiovascular disease. However, differences in factors that we were unable to measure, such as adherence to a drug regimen, differential prescribing of ADHD drugs to children at lower risk for a study outcome, or illicit use of medications resulting in misclassification, may have affected the results.[31,32]

We performed several alternative analyses to test the robustness of our findings. We used former users as the reference group, which could address many of the issues related to comparability between current users and nonusers. We performed an analysis restricted to new users to address bias that would be introduced from the inclusion of prevalent users in the cohort.[10] Another analysis included patients who had been excluded from the primary analysis because of preexisting severe cardiac disease for which sudden cardiac death would not be unexpected. We

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Table 3. Adjusted Hazard Ratios for Individual Cardiovascular End Points, According to the Use of ADHD Drugs.*

End Point	Person-Yr	Events	Rate per 100,000 Person-Yr	Hazard Ratio (95% CI)†
	number			
Sudden cardiac death				
Nonuser	1,597,962	17	1.06	1.00
Former user	607,475	13	2.14	1.52 (0.65–3.56)
Current user	373,667	3	0.80	0.88 (0.23–3.35)
Acute myocardial infarction				
Nonuser	1,597,962	6	0.38	1.00
Former user	607,475	3	0.49	0.88 (0.16–4.71)
Current user	373,667	0	0	NA
Stroke				
Nonuser	1,597,962	26	1.63	1.00
Former user	607,475	9	1.48	0.80 (0.33–1.96)
Current user	373,667	4	1.07	0.93 (0.29–2.97)

* For all comparisons, the reference group was nonusers of ADHD drugs. Hazard ratios were estimated with the use of Cox regression models, which were adjusted for the site-specific propensity-score decile, study site, medical conditions (serious cardiovascular disease and serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), age, and calendar year. Models were not calculated for acute myocardial infarction among current users because there were no events. NA denotes not applicable.

Table 4. Alternative Analyses with Adjusted Hazard Ratios for Serious Cardiovascular Events, According to the Use of ADHD Drugs.*

Analysis	Exposure	Reference	Hazard Ratio (95% CI)
Primary analysis	Current user	Nonuser	0.75 (0.31–1.85)
Analysis restricted to new users of ADHD medications†	New user	Nonuser	0.73 (0.24–2.10)
Analysis including patients with severe underlying cardiac disease‡	Current user	Nonuser	0.71 (0.29–1.72)
Analysis restricted to children 2–17 yr of age	Current user	Nonuser	0.98 (0.41–2.36)
Analysis restricted to children without evidence of a serious psychiatric disorder§	Current user	Nonuser	0.66 (0.20–2.16)

* Hazard ratios were estimated with the use of Cox regression models, which were adjusted for the site-specific propensity-score decile, study site, medical conditions (serious cardiovascular disease and serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), age, and calendar year.
† New users included patients who had not received ADHD drugs in the 365 days before the first day of qualifying use.
‡ For patients with severe underlying cardiac disease, sudden cardiac death would not be unexpected.
§ This analysis excluded cohort members who had any of the following at baseline or during follow-up: use of psychotropic medications (antipsychotic drugs, mood stabilizers, or lithium) or evidence of a treated mental illness (major depression, bipolar disorder, psychotic disorder, autism, or hospitalization with a psychiatric diagnosis).

also performed analyses stratified according to age. The findings from these additional analyses were essentially identical to our primary analysis.

Our findings that the use of ADHD drugs was not associated with an increased risk of serious cardiovascular events in children and young adults are consistent with the results of several reports[33-36] that have appeared since the FDA safety review of

adverse-event data for ADHD drugs,[6,7] although our results differed from the findings of another report.[37] Our study included nearly twice the person-time of the combined person-time in four recent cohort studies and included several provisions to ensure accurate case ascertainment, including a review of medical records and autopsies.

In conclusion, in our study involving children and young adults with 2.5 million person-years of follow-up, there were 3.1 serious cardiovascular events per 100,000 person-years. Although the point estimates of the relative risks for ADHD drugs did not indicate increased risk, the upper limit of the 95% confidence interval suggested that a doubling in the risk could not be ruled out. However, the absolute magnitude of any increased risk would be low.

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