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ABSTRACT

OBJECTIVES. Case reports have raised concerns about the risk of cardiac events associated with central nervous system stimulants for the treatment of attention-deficit/hyperactivity disorder.

PATIENTS AND METHODS. This was a retrospective cohort study that used 10 years (July 1994 to June 2004) of Florida Medicaid claims data cross-linked to Vital Statistics Death Registry data. The cohort was composed of all youth 3 to 20 years old who were newly diagnosed with attention-deficit/hyperactivity disorder. 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, including follow-up of youth who were never exposed to stimulants). The study’s end points were (1) cardiac death, (2) first hospital admission for cardiac causes or (3) first emergency department visit for cardiac causes. Risks were compared with time-dependent Cox regression analysis adjusting for various cardiac risk factors.

RESULTS. During 124,932 person-years of observation ($n = 55,383$), 73 youth died, 5 because of cardiac causes. No cardiac death occurred during 42,612 person-years of stimulant use. Hospital admissions for cardiac cause occurred for 27 children (8 during stimulant use, 11 during 35,671 person-years of former use, and 8 during 46,649 person-years of nonuse); and 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 visits when compared with nonuse. No increased risk was found for periods of former use when compared with nonuse.

CONCLUSIONS. Incidence rates of cardiac events requiring hospitalization were small and similar to national background rates. Stimulants were associated with an increase in cardiac emergency department visits. More evidence is needed that addresses the long-term risk/benefit of the various treatment options and the effect of other cardiac risk factors and comediations.
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). In response, the Pediatric Advisory Committee of the FDA suggested that a black-box warning may not be warranted. 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 known propensity of sympathomimetic agents to raise blood pressure and heart rate, the history of serious adverse effects associated with other sympathomimetic agents to raise blood pressure and heart rate, the history of serious adverse effects associated with other stimulant drugs used to treat ADHD, and the rapid increase in stimulant use, exposing a large population of children and adolescents.

Clinical evidence of the cardiac risk of stimulants approved for ADHD consists of placebo-controlled trial data that demonstrate an increase in blood pressure and heart rate, which is typically described as mild, of short duration, and responsive to dosing or timing adjustments, and several case reports of stroke, myocardial infarction, and sudden death to the FDA Adverse Event Reporting System. Twenty international reports of sudden death resulted in the withdrawal of Adderall XR from the Canadian market in February 2005; this decision was reached despite the concern that case reports deliver questionable proof of causality, especially because some case subjects showed on autopsy evidence of undiagnosed 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. The Canadian regulatory body revoked its decision 6 months later, which reflects the intensity of the current debate in the absence of solid clinical evidence.

This lack of evidence is even more significant considering that stimulants are now used chronically in >5% of American children and in a rapidly growing number of adults. Longitudinal comparisons suggest that both the diagnosis and treatment of childhood ADHD have continued to increase over the last decade and that approximately one third of newly treated children use treatment chronically for ≥2 years, and >15% continue for >5 years according to a recent analysis in this laboratory. Formal epidemiologic studies are overdue in light of the scarce long-term safety data, the growing prevalence of stimulant use, and the anecdotal evidence of serious adverse events. This study aimed to assess the risk of stimulants for adverse cardiac events in children and adolescents with ADHD.

PATIENTS AND METHODS
Study Design
A retrospective cohort design including 10 years (July 1994 to June 2004) of Medicaid claims data were used to estimate the incidence of cardiac outcomes in children with diagnosis of ADHD.

Data Sources
The data set was assembled from the Florida Medicaid fee-for-service program, representing the majority of patients eligible for Medicaid benefits in Florida, and included a total of 2,131,953 children and adolescents during the 10-year study period. Details on the demographic composition and stimulant use pattern of the study cohort are described elsewhere. The administrative data set encompasses an enrollment file specifying monthly eligibility along with demographic information and all of the claims adjudicated by Medicaid, including ambulatory, acute, and long-term health care encounters, as well as pharmacy claims and other auxiliary services. Information on death and causes of death was obtained from the Vital Statistics Death Registry and cross-linked to the Medicaid data. The study was approved by the University of Florida Institutional Review Board and received a waiver for Health Insurance Portability and Accountability Act authorization.

Study Population
We used data of all of the beneficiaries between 3 and 20 years of age who were enrolled between July 1994 and June 2004 who had ≥1 inpatient or outpatient claim for ADHD, defined as International Classification of Diseases, Ninth Revision (ICD-9), clinical modification (CM) code 314.xx. To be considered for analysis, the first diagnosis of ADHD and the first use of a stimulant had to occur after a minimum of 6 months of continuous Medicaid eligibility without a stimulant claim or ADHD diagnosis. For patients with interrupted eligibility for Medicaid, only the period with continuous eligibility when the first diagnosis occurred was used for analysis to ensure complete access to claims associated with adverse cardiac events.

Study End Points
Consistent with previously reported cases, the following end points were considered: (1) death from circulatory disease (ICD-9 390–459 or International Classification of Diseases, Tenth Revision, I00–I99 for records after 1999); (2) first hospital admission with principal diagnosis of acute myocardial infarction (ICD-9-CM 410.xx, 411.8xx), stroke (430.xx to 436.xx), hypertensive disease (401.xx to 405.xx, excluding malignant causes 40x.0), angina (413.xx), aortic or thoracic aneurysm (441.0x, 441.1x), and arrhythmias (426.89, 427.xx); (3) first emergency department (ED) visit for cardiac causes as defined above.
or for cardiac symptoms including syncope (780.2x), tachycardia, or palpitation (785.0x, 785.1x); and (4) first physician office visit for cardiac cause or cardiac symptoms.

Risk Factors for Cardiac Events

Patients with congenital anomalies of the heart and other hereditary diseases that are often associated with adverse events of the circulatory system were identified by the presence of an inpatient or outpatient claim at any time in the study period with any of the following diagnoses: hereditary hemolytic anemia (ICD-9-CM 282.xx), hemophilia (286.0x to 286.4x), anomalies of bulbus cordis and cardiac septal closure (745.xxx), 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 X syndrome (759.83).

Preexisting heart disease was defined as the presence of any inpatient or outpatient claim within 6 months before first ADHD diagnosis or first stimulant claim, whichever came first, with any of the following codes: diseases of the circulatory system (390.xx to 459.xx), syncope (780.2x), tachycardia or palpitation (785.0x, 785.1x), and chest pain (786.50). Using the same prediagnosis or pretreatment time period, 2 variables were used as proxies for general health status, namely, hospital admission for any cause and whether Medicaid eligibility was based on disability (aid to the disabled).

To account for the concurrent use of other drugs that have been associated with cardiac effects, we ascertained claims data of appetite suppressant drugs, monoamine-oxidase inhibitors, bronchodilators (β-agonists, ipratropium bromide, or theophylline analogs), antidepressants, and antipsychotic agents. No attempt was made to find claims for oral decongestants, because most decongestants 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 after the index date was classified according to stimulant use. The time preceding the first stimulant claim, including the follow-up months of all of the subjects who were never exposed to stimulants after ADHD diagnosis, was classified as “nonuse.” All of the months where a stimulant prescription was active were assigned to the “current use” period. Months after periods of current use were classified as “former use.” Patients were allowed to switch back and forth between former and current use.

The category “former use” was established because the characteristics of this group should be similar to those of current use and minimize differences in unmeasured patient characteristics that may be associated with the decision to use stimulants (confounding by indication).

Risk among the various groups was compared using a time-dependent Cox proportional hazard model to adjust for group differences in gender, race, Supplemental Security Income (eligibility as aid to the disabled), congenital anomalies, history of circulatory disease, history of hospital admission, and the use of antidepressants, antipsychotic agents, and bronchodilators as covariates.

Data Analysis

A new-user design was used where newly diagnosed patients entered the cohort at the first claim for ADHD or stimulant, whichever came first (index date). Both first diagnosis and drug claim had to be preceded by a 6-month period of continuous eligibility without any such claim. Patients were followed until the outcome of interest occurred, eligibility ended, the first diagnosis for malignant neoplasm occurred (defined by an inpatient or outpatient claim with ICD-9-CM 140.xx to 208.xx or 230.xx to 234.xx), or they turned 21 years of age, whichever came first.

The use of central nervous system stimulants was determined from pharmacy claims using generic codes for methylphenidate, amphetamine, dexamphetamine, and pemoline. All of the immediate and sustained release forms were included. Patients who used atomoxetine (n = 3702) or methamphetamine (n = 21) at any time during the study period were excluded from analysis, because atomoxetine is not classified as a stimulant, and methamphetamine is rarely used. 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.

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Three binary independent variables above versus below the age thresholds of 5, 10, and 15 years were used. Likewise, 3 independent variables for race or ethnicity, white versus nonwhite, black versus nonblack, and Hispanic versus non-Hispanic were used. Age and the use of antidepressant, antipsychotic agent, and asthma drugs were updated for every month of follow-up. All of the variables were entered in a stepwise-forward fashion and included if they showed an independent significant association with the clinical end point (P < .05). Adjusted incidence rates, defined as first event per patient-years of follow-up, were calculated for former use and current use using the crude incidence rate of nonuse multiplied by the respective adjusted hazard ratio (HR).

Data management and analysis were conducted with SAS 9.1 (SAS Institute, Cary, NC).

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Data management and analysis were conducted with SAS 9.1 (SAS Institute, Cary, NC).
RESULTS

The final cohort consisted of 55,383 patients with a qualifying new diagnosis of ADHD, 32,807 of these with claims for stimulants and 22,576 without any such claim (Table 1). Compared with patients without any stimulant claim during the study period, stimulant users (current or former users) were more likely to be male, White, non-Hispanic, and to use other psychotropic medications (antidepressants and antipsychotic agents). Patients in periods of current use were, on average, 1 year younger when compared with both those in former use and nonuse periods. The distribution of patients with a history of circulatory disease was similar among the groups.

Of a total of 124,932 person-years of observation, current stimulant use contributed 42,612 person-years, former use contributed 35,671 person-years, and nonuse contributed 46,649 person-years. Seventy-three children died over the study period, resulting in an all-cause mortality rate of 58.4 per 100,000 patient-years. The rank order of prevalent causes for death was accidents ($n/11005 21$), disease of the central nervous system ($n/11005 8$), homicide ($n/11005 7$), and disease of the circulatory system ($n/11005 5$). The rate of deaths because of circulatory causes was 4.0 per 100,000 person-years (Table 2). No cardiac sudden death occurred during 42,612 years of current stimulant use. Hospital admissions for cardiac disease occurred in 27 children (21.6 per 100,000 person-years), and 1091 children visited the ED for cardiac causes or symptoms at a rate of 8.7 per 1000 patient-years. The most prevalent causes for the target ED visits were syncope (33.7%), cardiac dysrhythmia (32.6%), tachycardia and palpitation (15.7%), and hypertensive disease (14.7%). Because of the small number of fatal and serious events requiring hospital admission, no attempt was made to compare incidence rates for those end points among the groups.

Stimulant use was associated with a 20% increase (adjusted HR: 1.20; 95% CI: 1.04–1.38) in the hazard for ED visits for cardiac causes or symptoms when compared with nonuse (Table 3). The former use of stimulants was not associated with an increased hazard when compared with nonuse (adjusted HR: 1.02; 95% CI: 0.86–1.20). The comparison of periods of current use with former use resulted in an adjusted HR of 1.17 (95% CI: 1.00–1.38). Associations between stimulant use and physician office visits for cardiac cause or symptoms were similar with a 21% increase (95% CI: 6%–39%) in the hazard during current-use periods when compared with nonuse periods.

Other risk factors for ED visits that were significant in the regression model were age with a lower hazard for children $<15$ years of age when compared with children $\geq 15$ years of age (HR: 0.62; 95% CI: 0.53–0.72), congenital anomalies (HR: 2.31; 95% CI: 1.84–2.90), history of circulatory disease (HR: 3.70; 95% CI: 2.96–4.63), disability (HR: 1.19; 95% CI: 1.04–1.35), and the use of antidepressants (HR: 1.80; 95% CI: 1.54–2.12), antipsychotic agents (HR: 1.48; 95% CI: 1.23–1.78), and bronchodilators (HR: 1.67; 95% CI: 1.37–2.03). Black children were less likely to visit the ED when compared with nonblack children (HR: 0.83; 95% CI: 0.72–0.94). Similar associations were observed for physician office visits.

Claims for monoamine-oxidase inhibitors were found in only 1 patient and occurred several months before

<p>| TABLE 1 Characteristics of Study Cohorts With and Without Stimulant Use |
|-----------------------------|-----------------------------|
| Characteristic              | Stimulant Use ($N = 32,807$) | Nonuse ($N = 22,576$)* |</p>
<table>
<thead>
<tr>
<th></th>
<th>Current Use</th>
<th>Former Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age at first assignment to group, mean (±SD), y</td>
<td>8.2 (±3.0)</td>
<td>9.1 (±3.1)</td>
</tr>
<tr>
<td>Use of bronchodilators, %</td>
<td>19.6</td>
<td>17.2</td>
</tr>
<tr>
<td>Use of antidepressants, %</td>
<td>23.6</td>
<td>18.8</td>
</tr>
<tr>
<td>Use of antipsychotic agents, %</td>
<td>14.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Average age at index date, mean (±SD), y</td>
<td>8.2 (±3.0)</td>
<td>9.3 (±3.9)</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>72.5</td>
<td>66.7</td>
</tr>
<tr>
<td>Race or ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>49.9</td>
<td>38.8</td>
</tr>
<tr>
<td>Black</td>
<td>29.6</td>
<td>30.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>14.5</td>
<td>24.8</td>
</tr>
<tr>
<td>Average follow-up time, mean (±SD), mo</td>
<td>31.2 (±27.4)</td>
<td>21.1 (±22.5)</td>
</tr>
<tr>
<td>Eligible as aid to disabled, %</td>
<td>22.4</td>
<td>20.7</td>
</tr>
<tr>
<td>Circulatory disease, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>2.2</td>
<td>1.8</td>
</tr>
<tr>
<td>History of circulatory disease/symptoms</td>
<td>1.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Previous hospital admission for any cause</td>
<td>2.5</td>
<td>3.8</td>
</tr>
</tbody>
</table>

* Data include only patients without any stimulant claim during the follow-up period; for inferential analyses, months preceding the first stimulant claim of users were added to the nonuse period.
stimulant exposure. No patient had claims for appetite suppressants. Only 10 of the 1091 ED visits included an ICD-9-CM code for stimulant poisoning (969.7–969.9, 970.8, 970.9, and 977.0), and none was identified as addiction to stimulants (304.4).

**DISCUSSION**

Two important findings emerge from this study. First, the use of stimulants was associated with an increased incidence of ED and physician office visits for cardiac symptoms. Second, the incidence of fatal and serious events because of circulatory causes in the study population was low and seemed similar to national background rates. The 2002 national hospital discharge rate was low and seemed similar to national back-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Person-Years</th>
<th>Events</th>
<th>Adjusted Rate (Events per 1000 Patient-Years)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ED visit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>42,612</td>
<td>406</td>
<td>10.9</td>
<td>1.20 (1.04–1.38)</td>
</tr>
<tr>
<td>Former use</td>
<td>35,671</td>
<td>261</td>
<td>9.3</td>
<td>1.02 (0.86–1.20)</td>
</tr>
<tr>
<td>Nonuse</td>
<td>46,649</td>
<td>424</td>
<td>9.1</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Physician office visit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>42,637</td>
<td>440</td>
<td>13.1</td>
<td>1.21 (1.06–1.39)</td>
</tr>
<tr>
<td>Former use</td>
<td>35,479</td>
<td>291</td>
<td>10.4</td>
<td>0.96 (0.83–1.12)</td>
</tr>
<tr>
<td>Nonuse</td>
<td>46,399</td>
<td>503</td>
<td>10.8</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data were adjusted for significant risk factors including age, race or ethnicity, congenital anomalies, history of circulatory disease, disability, and concomitant use of antidepressants, antipsychotic agents, and bronchodilators.

research perspective but also poses questions for the interpretation of clinical significance. Moreover, the ability to answer whether chronic exposure to stimulants results in long-term manifestation of heart disease may depend on follow-up data that span longer time periods. Our study cannot rule out that children treated for several years with stimulants might be at increased risk for cardiac disease in adulthood.

The reassuring findings as reflected in a low potential risk for fatal and serious manifestations of heart disease notwithstanding, the detected increase in ED visits deserves discussion. Several methodologic considerations important to the interpretation of the results ought to be mentioned. First, although our multivariate analysis showed that we successfully adjusted for selected cardiac risk factors, unmeasured 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 or appetite suppressants, or the presence of undiagnosed congenital heart disease. Thus, a direct comparison between nonuse and current-use periods may be biased. The additional analysis of former use mitigates such bias, because the hazard rates of periods of former use (ie, patients who had received stimulants in the past) and of nonuse (ie, patients who had not received stimulants) were almost identical after the described adjustments were made. In other words, subjects diagnosed with ADHD who were never exposed to stimulants had a similar risk for cardiac ED visits as subjects who used to receive stimulants, but the risk increased during periods of stimulant exposure.

The decision to use stimulants may be related to the severity of ADHD and the presence of comorbidities. ADHD has not been associated with cardiac symptoms, but some studies have suggested that anxiety and panic attack disorder can result in increased sympathetic activity and decreased cardiac vagal activity. Patients with comorbidities such as depression or anxiety may also have a limited ability to cope with potentially minor symptoms (eg, anxiety in the presence of tachycardia).
or the underlying mental disease may not be recognized when patients present in the ED.\textsuperscript{24,25} We identified 5612 patients with a diagnosis for anxiety disorders at any time during the follow-up period. The presence of the diagnosis was independently associated with an increase in cardiac ED visits (HR: 1.45; 95% CI: 1.25–1.68) but did not change the HR for stimulants (HR: 1.21; 95% CI: 1.05–1.39). Likewise, the inclusion of the total number of unique mental health diagnoses as covariates in the Cox regression model as a proxy for case severity did not show any association with ED visits and did not change the HR for stimulants.

Pharmacoepidemiologic studies ideally should be informed by both a pharmacologic causal model and a health care pathway model, including patient- and provider-specific aspects of health care decision-making.\textsuperscript{26} Considering the latter, one could argue that ED visits may vary in clinical severity and reflect parent concern and other sociocultural aspects rather than the manifestation of adverse events. Specifically, the knowledge of potential cardiac adverse effects of stimulants may result in a greater propensity to seek health care when even minor symptoms present. Thus, the fear of adverse effects may have resulted in some ED visits, whereas unexposed children with similar symptoms may have received no medical attention. This bias would be critical for studies conducted in the last 2 years when reports about cardiac adverse effects were heavily debated and ultimately resulted in the recent FDA mandates, but these concerns were rarely voiced before 2004. Considering the clinical significance of ED visits, some may argue that ED visits contribute a larger proportion to ambulatory health care use in patients with Medicaid benefits when compared with commercial plans.\textsuperscript{27} However, case acuity has not shown significant differences, with \textasciitilde{}40% to 44% of all ED visits labeled urgent in Medicaid beneficiaries compared with 44% to 47% of visits covered under private plans.\textsuperscript{28}

Second, determination of drug exposure and cardiac events relied on claims data, which may have resulted in misclassification error. For example, some cardiac events may have been missed, or the designation of youth as stimulant users or nonusers may have been incorrect in some instances. Both scenarios would result in a decreased ability to detect safety problems. For example, the attribution of stimulant-related events to former use would bias the HR toward 1, thus resulting in an under-estimate of the association between stimulants and adverse events. The underestimation of cardiac events would result in decreased power to detect statistically significant differences among groups.

Last, we decided to restrict our cohort to ADHD incident cases to protect the analysis from healthy survivor bias, that is, stimulant users who enter the study after a period of exposure are likely to represent patients who tolerate treatment. Thus, this analysis evaluates the treatment effect in previously stimulant-naïve patients and should circumvent any bias related to switching or discontinuing treatment. Despite the various methodologic safeguards, it is important to note that our study is based on nonexperimental data and, as such, is not able to establish causality.

Two reports on stimulant-related ED visits that provide national estimates have been published. Cohen et al\textsuperscript{29} estimated on the basis of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project that, in 2004, \textasciitilde{}3075 patients visited the ED nationally because of adverse events from stimulants used for the treatment of ADHD, excluding abuse or intentional self-harm. The Drug Abuse Warning Network projected in its 2004 report that \textasciitilde{}102 000 ED visits nationally were caused by the illicit use of stimulants, and 2642 ED visits were attributable to methylphenidate and amphetamine or dexamphetamine used for medical reasons.\textsuperscript{30,31} Both surveillance systems rely on the medical recognition and documentation of drug effects when patients present with symptoms and may underestimate the true incidence. Assuming that our estimated excess stimulant risk of 1.6 cardiac ED visits per 1000 patient-years can be generalized to the 2.5 million youth between the ages of 4 and 17 years who were taking medication for ADHD in 2003,\textsuperscript{16} \textasciitilde{}4000 ED visits would be attributable to stimulants nationwide.

In summary, given the clinical trial data that demonstrate a stimulant effect on heart rate and blood pressure,\textsuperscript{4–8} it is not surprising that our analysis finds an association between stimulant use and ED visits for similar types of symptoms. Whether these symptoms manifest in heart disease is unclear, but our data suggest that such a manifestation is likely rare within the age group and follow-up time period studied. Several questions arise from our findings. First, stimulant risk for manifestation of severe heart disease should be addressed. This would be a challenging investigation in light of the volume of records needed to compare small incidence rates.

\begin{table}[h]
\centering
\caption{Incidence of Study End Points (Count of Children With \textasciitilde{}1 Event per Follow-up Time)}
\begin{tabular}{llll}
\hline
\textbf{Variable} & \textbf{No Stimulant Use} & \textbf{Former Stimulant Use} & \textbf{Current Stimulant Use} \\
\hline
Person-years of follow-up & 46,649 & 35,671 & 42,612 \\
Circulatory death & 2 & 3 & 0 \\
Myocardial infarction or stroke & 1 & 2 & 5 \\
Hospital admission for circulatory disease & 8 & 11 & 8 \\
ED visit for circulatory disease or cardiac symptoms & 424 & 261 & 406 \\
Physician office visit for circulatory disease or cardiac symptoms & 503 & 440 & 291 \\
\hline
\end{tabular}
\end{table}
Special scientific attention should be given to patient populations with elevated risk for heart disease, such as adults and those treated off label for poststroke depression. Considering the long-term impact of hypertension on cardiac disease, consequences of chronic stimulant exposure during childhood may manifest decades later, and prospective studies will require extensive follow-up periods. Second, recommendations for risk management strategies ought to be developed, such as the recently released FDA direction to manufacturers to develop patient medication guides. Third, whereas our study assumed a drug class effect, differences might exist between drugs or formulations, and exploration of these differences should be a priority. The presence of a drug class effect is supported by the 2005 FDA advisory committee conclusions that blood pressure changes represented such a reliable predictor of cardiovascular outcomes that class labeling would be appropriate in most cases. It is also consistent with the case reports of cardiac sudden death, which included both amphetamines and methylphenidate. Although atomoxetine is not classified as a stimulant, it does increase the availability of norepinephrine in neurons and has been shown to result in elevations in heart rate and blood pressure. Given the different pharmacological mechanisms in sympathomimetic activity, atomoxetine was not included in this analysis, but additional research investigating this drug would be prudent. Last, assessment of the prescribing and drug taking behavior since 2005, when safety concerns about stimulants were voiced, would be important for the understanding of the impact of safety recommendations on the treatment of ADHD.

CONCLUSIONS

Incidence rates of fatal or serious manifestation of heart disease requiring hospitalization were small and similar to national background rates. Stimulants were associated with an increase in ED and physician office visits for cardiac symptoms. More evidence is needed that addresses the long-term risk/benefit of the various treatment options and the effect of other cardiac risk factors and comediations.

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