Cardiovascular Events and Death in Children Exposed and Unexposed to ADHD Agents

WHAT'S KNOWN ON THIS SUBJECT: Attention-deficit/hyperactivity disorder agents increase systolic and diastolic blood pressure and heart rate. Case reports of sudden death in children and adolescents receiving these agents have led to the concern that they might increase the risk of cardiovascular events.

WHAT THIS STUDY ADDS: Low rates of validated cardiovascular events and of all-cause death, nonsuicide, and non–accidental death were found in children and adolescents receiving attention-deficit/hyperactivity disorder medications.

abstract

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OBJECTIVE: The objective of this study was to compare the rate of severe cardiovascular events and death in children who use attention-deficit/hyperactivity disorder (ADHD) medications versus nonusers.

PATIENTS AND METHODS: We performed a large cohort study using data from 2 administrative databases. All children aged 3 to 17 years with a prescription for an amphetamine, atomoxetine, or methylphenidate were included and matched with up to 4 nonusers on the basis of data source, gender, state, and age. Cardiovascular events were validated using medical records. Proportional hazards regression was used to calculated hazard ratios.

RESULTS: We identified 241 417 incident users (primary cohort). No statistically significant difference between incident users and nonusers was observed in the rate of validated sudden death or ventricular arrhythmia (hazard ratio: 1.60 [95% confidence interval (CI): 0.19–13.60]) or all-cause death (hazard ratio: 0.76 [95% CI: 0.52–1.12]). None of the strokes identified during exposed time to ADHD medications were validated. No myocardial infarctions were identified in ADHD medication users. No statistically significant difference between prevalent users and nonusers (secondary cohort) was observed (hazard ratios for validated sudden death or ventricular arrhythmia: 1.43 [95% CI: 0.31–6.61]; stroke: 0.89 [95% CI: 0.11–7.11]; stroke/myocardial infarction: 0.72 [95% CI: 0.09–5.57]; and all-cause death: 0.77 [95% CI: 0.56–1.07).

CONCLUSIONS: The rate of cardiovascular events in exposed children was very low and in general no higher than that in unexposed control subjects. Because of the low number of events, we have limited ability to rule out relative increases in rate. *Pediatrics* 2011;127:1102–1110

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KEY WORDS

children, adolescents, amphetamines, atomoxetine, methylphenidate, cardiovascular, death

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder
MI—myocardial infarction
ICD-9—*International Classification of Diseases, Ninth Revision*
PPV—positive predictive value
CI—confidence interval
HR—hazard ratio

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The study's sponsor approved the protocol and had the right to provide nonbinding written comments on a draft of the manuscript. The authors independently performed and analyzed the study and wrote the manuscript.

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Attention-deficit/hyperactivity disorder (ADHD) medications (amphetamines, atomoxetine, and methylphenidate) were taken by 2.7 million [4.8%] children aged 4 to 17 years in the United States in 2007.[1] These agents can increase systolic and diastolic blood pressure (on average 1–4 mm Hg) and heart rate (on average 3–8 beats per minute).[2–4] Case reports of sudden death in children and adolescents receiving these agents have led to the concern that they might increase the risk of cardiovascular events, especially in those with structural cardiac abnormalities or other serious heart problems. To date, 3 studies[5–7] have tried to evaluate the association between exposure to ADHD medications in children and adolescents and cardiovascular events. However, results have been inconclusive.

Given the public concern about the cardiovascular safety of ADHD medications,[8] the aim of this cohort study was to compare the incidence rate of serious cardiovascular events in a large population of children and adolescents dispensed ADHD medications versus unexposed, population-based reference groups. On the basis of existing safety concerns, the prespecified events of primary interest were (1) sudden death or ventricular arrhythmia, (2) stroke, (3) myocardial infarction (MI), and (4) a composite end point of stroke or MI. Prespecified secondary end points were (1) all-cause death, (2) nonaccidental death, and (3) nonsuicide death. The rationale for studying all-cause death is that ascertainment is complete and unbiased (whereas cardiovascular diagnoses might be incomplete and potentially subject to ascertainment bias) and it is itself important. The rationale for studying nonaccidental and nonsuicide death was to eliminate causes of death that seemed unlikely to be caused by ADHD medications.

PATIENTS AND METHODS

Data Source

This investigator-initiated cohort study used preexisting administrative data. Its design and rationale are described in detail elsewhere.[9] In brief, we used data from 2 US populations (ie, a 5-state Medicaid database [1999–2003] and the 14-state HealthCore Integrated Research Database [2001–2006]). In addition, we included linked Medicare data on Medicaid-Medicare dual eligibles. The HealthCore Integrated Research Database contains health insurance claims from 1 of the largest commercial insurers in the United States. The study was approved by the University of Pennsylvania's Committee on Studies Involving Human Beings, which granted waivers of informed consent and Health Insurance Portability and Accountability Act authorization.

Study Subjects

We identified all subjects aged 3 to17 years who were dispensed a solid oral dosage form of the following ADHD medication classes: (1) amphetamines (of which 87% were mixed amphetamine salts); (2) atomoxetine; (3) methylphenidate; and (4) any of these ADHD medication classes (ie, amphetamines, atomoxetine, methylphenidate, or combination therapy). The primary cohort consisted of incident users, defined as those with at least 180 days of observation before their first ADHD medication prescription. A secondary cohort consisted of prevalent users, defined as those with fewer than 180 days of observation before their first observed ADHD medication prescription. The rationale for making incident users our primary cohort was to avoid bias toward the null caused by the depletion of susceptible subjects.[10] Each ADHD medication user was matched on the basis of data source, age in 3-year bands, state, and gender with up to 4 subjects aged 3 to 17 years who never had a prescription filled for an ADHD medication and had at least 180 days of continuous baseline eligibility.

Eligible Person-Time

Follow-up started for users and nonusers immediately after the 180-day baseline period. For incident users, the baseline period was the 180-day period immediately preceding the first dispensed ADHD medication. For the secondary analysis in prevalent users, the baseline period was the first 180 days after enrollment.

In the exposed groups, we included only person-time during an active study prescription, because including unexposed time would bias results toward the null. In our data, the median duration of an ADHD medication prescription according to the day's supply field was 30 days, and the median time between fill dates of consecutive prescriptions for each ADHD medication class ranged from 32 to 38 days. Therefore, we assumed that the duration of an active study prescription was 30 days, unless a subsequent prescription occurred sooner. We also performed sensitivity analyses, assuming that each prescription lasted for a maximum of 60, 90, and 120 days. The rationale for these sensitivity analyses was to allow for nonadherence and include events that may have occurred shortly after cessation of therapy. In the unexposed groups, we included all postbaseline person-time before a censoring event.

Follow-up was censored with the earliest of the following: (1) the first event of interest (for the analysis of that event); (2) the end of the last observed prescription period for exposed subjects; (3) disenrollment from the health care plan; (4) the end of the study period; or (5) death. In addition, in the analyses of individual ADHD med-

ication classes, we censored ADHD medication users when they switched to or added a different ADHD medication class. In the analyses of exposure to any ADHD medication, a user was considered exposed to an ADHD medication even if they switched or used 2 study drugs concomitantly. Because reinitiators might have a lower cardiovascular risk than incident users (because they survived the initial course), we performed a sensitivity analysis in which we censored users of individual classes when they had a gap of 180 days or more between consecutive prescriptions of the same ADHD medication class.

Events of Interest

We studied the following claims-based outcomes: (1) hospitalization or emergency-department visit with a first-listed diagnosis of sudden cardiac death or ventricular arrhythmia (*International Classification of Diseases, Ninth Revision* [ICD-9] codes 427.1, 427.4, 427.41, 427.42, 427.5, 798.1, and 798.2); (2) hospitalization with a first-listed diagnosis of stroke (ICD-9 codes 430, 431, 433.x1, 434 [excluding 434.x0], and 436); (3) hospitalization with a first-listed diagnosis of MI (ICD-9 code 410); and (4) composite outcome of hospitalization with either a first-listed diagnosis of stroke or MI (stroke/MI). Individuals who had a secondary-listed diagnosis for an event of interest recorded were censored on the day that this diagnosis was assigned. The rationale for this decision was that the first-listed diagnosis is purportedly the diagnosis chiefly responsible for the admission and/or emergency-department visit and has higher positive predictive values (PPVs) in adults.[11–20]

Although claim-based principal diagnoses for these outcomes have been shown to have PPVs of 70% to 94% in adults,[11–20] their validity had not been measured in children and adolescents. Therefore, we studied the validity of these outcomes by requesting all hospital or emergency-department medical records for those events. Each record obtained was reviewed independently by 2 pediatric neurologists (for stroke) or 2 pediatric cardiologists (for sudden death or ventricular arrhythmia and MI), who classified each event as probable or definite (considered true events), possible, or uncertain or unlikely on the basis of the expert's global clinical judgment. If the 2 experts disagreed, a third expert broke the tie. Events that did not validate were considered censoring events.

Secondary outcomes of interest were all-cause death, nonaccidental death (excluding ICD-10 codes V01–X57 [but not X43, X44, and X49]), and nonsuicide death (excluding ICD-10 codes X60–X84 and Y87.0). Deaths were ascertained using the Social Security Index Death Masterfile. To limit the costs of obtaining cause-of-death codes, we requested cause-of-death diagnosis codes from the National Death Index to identify nonsuicide and nonaccidental deaths after truncating person-time on the basis of the individual matching.

Statistical Analyses

After descriptive analyses and calculation of incidence rates with 95% confidence intervals (CIs), proportional hazards regression[21] was used to calculate unadjusted hazard ratios (HRs) for each ADHD medication class versus its matched unexposed group. The analyses of nonaccidental death and nonsuicide death were conditioned on matched set because we truncated person-time for those outcomes on the basis of the individual matching.

Baseline variables considered to be potential confounders are listed in the Supplemental Appendix. Because the low number of events did not permit adjustment via multivariable models, we adjusted for potential confounding through exclusion. In particular, we performed subanalyses excluding subjects with any potential confounding disease or drug use that changed the data source–adjusted HR of an ADHD medication by 10% or more. Because there was no pretreatment period in prevalent users during which to ascertain baseline variables, and because adjusting for a consequence of exposure can introduce bias,[22] we did not adjust for diagnosis- or drug-based variables in the analyses of prevalent users. PPVs and incidence rates with exact 95% CIs were calculated using Stata 11 (Stata Corp, College Station, TX); proportional hazards regression was performed using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

We identified 93 470 incident users of amphetamines, 19 830 of atomoxetine, 128 117 of methylphenidate, and 965 668 matched nonusers. Because users contributed person-time only during active ADHD medication prescriptions, they had a shorter median follow-up time than nonusers (135 days vs 609 days). Baseline characteristics of incident ADHD users and matched nonusers are shown in Table 1. Incident users had a higher frequency of mental health disorders (eg, anxiety and depression) and cardiovascular conditions and/or cardiovascular risk factors and were more likely to receive prescription medications in general. The most common cardiovascular disease/risk factors were hypercholesterolemia (0.4% in ADHD medication users and 0.1% in nonusers) and diabetes (0.3% in ADHD medication users and 0.2% in nonusers).

Outcome Validation

We identified 71 hospital and 212 emergency-department claims for sudden death or ventricular arrhyth-

TABLE 1 Baseline Characteristics of Incident ADHD Medication Users and Their Matched Non-ADHD Medication Users Aged 3 to 17 Years, Stratified According to Type of ADHD Medication

Baseline Variables	Amphetamine Users, $n = 93\,470$ (%)	Amphetamine Nonusers, $n = 373\,880$ (%)	*P*	Atomoxetine Users, $n = 19\,830$ (%)	Atomoxetine Nonusers, $n = 79\,320$ (%)	*P*	Methylphenidate Users, $n = 128\,117$ (%)	Methylphenidate Nonusers, $n = 512\,468$ (%)	*P*
Follow-up time, median (interquartile range), d	90 (30–240)	582 (216–1312)	<.001	60 (30–145)	610 (244–1038)	<.001	91 (30–238)	611 (216–1371)	<.001
Age, median (interquartile range), y	9 (7–12)	9 (7–13)	.125	11 (8–14)	11 (8–14)	.034	9 (7–12)	9 (7–12)	<.001
Female	26 124 (27.9)	104 496 (27.9)	1.000	6052 (30.5)	24 208 (30.5)	1.000	34 960 (27.3)	139 840 (27.3)	1.000
HealthCore Integrated Research Database enrollees	23 841 (25.5)	95 364 (25.5)	1.000	11 109 (56.0)	44 436 (56.0)	1.000	35 140 (27.4)	140 560 (27.4)	1.000
Race[a]			<.001			<.001			<.001
White	40 415 (58.0)	107 584 (38.6)		5902 (67.7)	15 082 (43.2)		48 275 (51.9)	134 797 (36.2)	
Black	13 157 (18.9)	77 468 (27.8)		1278 (14.7)	10 157 (29.1)		19 342 (20.8)	96 247 (25.9)	
Hispanic	8395 (12.1)	67 255 (24.1)		883 (10.1)	6661 (19.1)		15 720 (16.9)	101 997 (27.4)	
Other	7662 (11.0)	26 209 (9.4)		658 (7.5)	2984 (8.6)		9640 (10.4)	38 867 (10.5)	
Claim received with an ADHD diagnosis[b]	68 863 (73.7)	8270 (2.2)	<.001	13 092 (66.0)	1404 (1.8)	<.001	94 257 (73.6)	11 192 (2.2)	<.001
Any inpatient or outpatient claim during the baseline period	86 940 (93.0)	309 014 (82.7)	<.001	17 875 (90.1)	56 561 (71.3)	<.001	118 440 (92.4)	416 999 (81.4)	<.001
Cardiovascular disease/risk factors[c]	950 (1.0)	1901 (0.5)	<.001	288 (1.5)	436 (0.0)	<.001	1353 (1.1)	2503 (0.5)	<.001
Treatment for cardiovascular disease/risk factors[d]	5423 (5.8)	2446 (0.7)	<.001	1114 (5.6)	629 (0.8)	<.001	5031 (3.9)	3169 (0.6)	<.001
Congenital heart disease	317 (0.3)	632 (0.2)	<.001	76 (0.4)	156 (0.2)	<.001	398 (0.3)	968 (0.2)	<.001
Electrocardiogram	604 (0.6)	875 (0.2)	<.001	247 (1.2)	367 (0.5)	<.001	795 (0.6)	1197 (0.2)	<.001
Antipsychotic agent	6104 (6.5)	1441 (0.4)	<.001	1593 (8.0)	357 (0.5)	<.001	6671 (5.2)	2056 (0.4)	<.001
Antiseizure agent	2338 (2.5)	1567 (0.4)	<.001	636 (3.2)	339 (0.4)	<.001	2408 (1.9)	2183 (0.4)	<.001
Anxiolytic agent	1131 (1.2)	896 (0.2)	<.001	282 (1.4)	235 (0.3)	<.001	1223 (1.0)	1138 (0.2)	<.001
Aspirin	28 (0.0)	54 (0.0)	.001	[e]	13 (0.0)	.094	47 (0.0)	92 (0.0)	<.001
Bronchodilator	9655 (10.3)	23 334 (6.2)	<.001	1896 (9.6)	5193 (6.5)	<.001	12 893 (10.1)	33 119 (6.5)	<.001
Bupropion	2666 (2.9)	497 (0.1)	<.001	697 (3.5)	162 (0.2)	<.001	2878 (2.2)	670 (0.1)	<.001
Cyclooxygenase2 inhibitor	74 (0.1)	100 (0.0)	<.001	28 (0.1)	35 (0.0)	<.001	104 (0.1)	122 (0.0)	<.001
Inhaled corticosteroid	3197 (3.4)	5706 (1.5)	<.001	748 (3.8)	1592 (2.0)	<.001	4300 (3.4)	8706 (1.7)	<.001
Nonsteroidal anti-inflammatory drug	4559 (4.9)	12 116 (3.2)	<.001	910 (4.6)	2170 (2.7)	<.001	6514 (5.1)	17 303 (3.4)	<.001

[a] Only available for the Medicaid population.

[b] Measured during baseline and follow-up time.

[c] Cardiovascular disease/risk factors refer to sudden death or ventricular arrhythmia, MI, stroke, cardiomyopathy, diabetes, heart failure, hypercholesterolemia, hypertension, and ischemic heart disease.

[d] Treatment for cardiovascular disease/risk factors are use of angiotensin-converting enzyme inhibitors, use of aldosterone inhibitor, use of antiadrenergic agent, use of antiarrhythmic agent, use of antidiabetes agent, use of antihyperlipidemic agent, use of $\beta 2$ blocker, use of calcium channel blocker, use of loop diuretics, use of nitrate, use of thiazide diuretic, and use of a vasodilator.

[e] Omitted per Centers for Medicare and Medicaid Services Privacy Policy.

mia, 142 hospital claims for stroke, and 25 hospital claims for MI in users and nonusers. We were able to identify the hospital for 66 (93%) hospital and 99 (47%) emergency-department claims for sudden death or ventricular arrhythmia, 134 (94%) claims for stroke, and 23 (92%) claims for MI and requested the records corresponding to those events. In total, we received 155 (48%) of the requested records. The retrieval rate was 49% in users and 46% in nonusers. The retrieval rate was higher in the HealthCore Integrated Research Database (56%) than Medicaid (31%). The main causes of nonretrieval were the hospital did not respond (29%), the hospital declined to participate (29%), and the hospital had no record of the patient based on the information provided (25%).

The 2 independent reviews agreed in 84% of the sudden-death and ventricular arrhythmia records, 89% of the stroke records, and 67% of the MI records. The remaining records were reviewed by a third expert to break the tie. The PPV was 41% (95% CI: 30–52) for sudden death or ventricular arrhythmia, 41% (95% CI: 29–54) for stroke, and 50% (95% CI: 21–79) for acute MI. Most of the false-positive cases of sudden death or ventricular arrhythmia and stroke were attributed to trauma (eg, car crashes). On the basis of these low PPVs, subsequent analyses focused on validated cases of the cardiovascular outcomes and death events.

Validated and Death Events in Incident Users (Primary Analyses)

The crude incidence rates of the validated outcomes and of death were low (Table 2). Several of the HRs were inestimable because there were no events during ADHD medication exposed time. The HRs for validated sudden death or ventricular arrhythmia in incident users of methylphenidate and of any

TABLE 2 Incident ADHD Medication Users Versus Nonusers and the Rate of Validated Cardiovascular Events and of Death Events

Exposure	No. of Validated Events in ADHD Medication Users	Crude Incidence Rate per 10 000 Person-Years in ADHD Medication Users (95% CI)	No. of Validated Events in Non-ADHD Medication Users	Crude Incidence Rate per 10 000 Person-Years in Non-ADHD Medication Users (95% CI)	Data Source–Adjusted HR (95% CI)	Interaction by Data Source *P*
Sudden death or ventricular arrhythmia						
Amphetamines	0	0.00 (0.00–0.79)	[b]	0.04 (0.01–0.11)	Inestimable	—
Atomoxetine	0	0.00 (0.00–5.80)	[b]	0.06 (0.02–0.35)	Inestimable	—
Methylphenidate	[b]	0.16 (0.00–0.89)	[b]	0.05 (0.02–0.11)	2.63 (0.29–23.69)	1.000
Any ADHD medication	[b]	0.06 (0.00–0.36)	[b]	0.04 (0.02–0.08)	1.60 (0.19–13.60)	.993
Stroke						
Amphetamines	0	0.00 (0.00–0.79)	[b]	0.04 (0.01–0.11)	Inestimable	—
Atomoxetine	0	0.00 (0.00–5.80)	0	0.00 (0.00–0.23)	Inestimable	—
Methylphenidate	0	0.00 (0.00–0.59)	[b]	0.06 (0.03–0.13)	Inestimable	—
Any ADHD medication	0	0.00 (0.00–0.24)	[b]	0.05 (0.02–0.09)	Inestimable	—
MI						
Amphetamines	0	0.00 (0.00–0.79)	[b]	0.01 (0.00–0.07)	Inestimable	—
Atomoxetine	0	0.00 (0.00–5.80)	0	0.00 (0.00–0.23)	Inestimable	—
Methylphenidate	0	0.00 (0.00–0.59)	0	0.00 (0.00–0.03)	Inestimable	—
Any ADHD medication	0	0.00 (0.00–0.24)	[b]	0.00 (0.00–0.03)	Inestimable	—
Composite end point of stroke or MI						
Amphetamines	0	0.00 (0.00–0.79)	[b]	0.05 (0.01–0.13)	Inestimable	—
Atomoxetine	0	0.00 (0.00–5.80)	0	0.00 (0.00–0.23)	Inestimable	—
Methylphenidate	0	0.00 (0.00–0.59)	[b]	0.06 (0.03–0.13)	Inestimable	—
Any ADHD medication	0	0.00 (0.00–0.24)	11	0.05 (0.03–0.10)	Inestimable	—
All-cause death						
Amphetamines	12	2.57 (1.33–4.49)	274	3.55 (3.14–3.99)	0.95 (0.52–1.71)	.967
Atomoxetine	0	0.00 (0.00–5.80)	31	1.93 (1.31–2.74)	Inestimable	—
Methylphenidate	[b]	1.27 (0.55–2.50)	301	2.77 (2.47–3.11)	0.61 (0.30–1.25)	.560
Any ADHD medication	28	1.79 (1.19–2.59)	607	3.00 (2.77–3.25)	0.76 (0.52–1.12)	.503
Nonaccidental death[c]						
Amphetamines	[b]	0.87 (0.24–2.24)	29	1.95 (1.31–2.80)	0.41 (0.14–1.19)	1.000
Atomoxetine	0	0.00 (0.00–5.87)	[b]	1.35 (0.28–3.94)	Inestimable	1.000
Methylphenidate	[b]	0.81 (0.26–1.89)	18	0.89 (0.53–1.40)	0.85 (0.31–2.32)	1.000
Any ADHD medication	12	0.79 (0.41–1.38)	67	1.40 (1.08–1.77)	0.53 (0.29–0.99)	1.000
Nonsuicide death[c]						
Amphetamines	[b]	1.75 (0.76–3.45)	40	2.69 (1.92–3.67)	0.60 (0.28–1.29)	1.000
Atomoxetine	0	0.00 (0.00–5.87)	[b]	1.80 (0.49–4.61)	Inestimable	1.000
Methylphenidate	[b]	1.13 (0.46–2.33)	34	1.67 (1.16–2.34)	0.68 (0.30–1.54)	1.000
Any ADHD medication	21	1.40 (0.85–2.11)	96	2.00 (1.62–2.44)	0.65 (0.40–1.04)	1.000

[a] Cardiovascular condition refers to sudden death or ventricular arrhythmia, stroke, MI, cardiomyopathy, congenital heart disease, diabetes, heart failure, hypercholesterolemia, hypertension, ischemic heart disease, use of angiotensin-converting enzyme inhibitors, use of aldosterone inhibitor, use of antiadrenergic agent, use of antiarrhythmic agent, use of antidiabetes agent, use of antihyperlipidemic agent, use of β-blocker, use of calcium channel blocker, use of loop diuretics, use of nitrate, use of thiazide diuretic, and use of a vasodilator.
[b] Omitted per Centers for Medicare and Medicaid Services Privacy Guideline policy.
[c] These analyses were performed using proportional hazard regression conditioned on the matching variables.

ADHD medication were not statistically elevated compared with unexposed subjects, albeit with very wide 95% CIs that one would expect with such uncommon outcomes (HR: 2.63 [95% CI: 0.29–23.69] and HR: 1.60 [95% CI: 0.19–13.60], respectively). None of the validated strokes occurred during exposure to an ADHD medication. There were no MIs identified during ADHD medication exposure. Of the secondary outcomes, initiation of any ADHD medication was associated with a barely statistically significant reduced hazard of nonaccidental death (Table 2). The other HRs for all-cause, nonaccidental, and nonsuicide death were numerically less than 1, although all the corresponding 95% CIs included 1 (Table 2).

Adjustment via exclusion of each confounder 1 at a time did not result in significantly elevated HRs (data not shown). Exclusion of patients with a preexisting cardiovascular condition resulted in similar or attenuated HRs (data not shown).

Assuming that the maximum duration of an ADHD medication prescription was

60, 90, or 120 days and censoring users with a gap of 180 days or more between consecutive prescriptions of the same ADHD medication class produced similar or attenuated HRs (data not shown).

Validated and Death Events in Prevalent Users (Secondary Analysis)

We identified 68 552 prevalent amphetamine users, 10 951 prevalent atomoxetine users, 115 774 prevalent methylphenidate users, and 221 278 prevalent users of any ADHD medication. Their median postbaseline follow-up time was 160, 110, 158, and 210 days, respectively.

Table 3 presents the results of the analyses of validated and death events in prevalent ADHD medication users and nonusers. Many of the HRs were inestimable because there were no events in users or nonusers. Prevalent use of methylphenidate or any ADHD medication was not significantly associated with sudden death or ventricular arrhythmia, albeit with large 95% CIs that one would expect with uncommon outcomes (HR: 1.30 [95% CI: 0.15–11.14] and HR: 1.43 [95% CI: 0.31–6.61], respectively). No increased hazard was observed for stroke (HR: 0.89 [95% CI: 0.11–7.11]) or stroke/MI (HR: 0.72 [95% CI: 0.09–5.57]) during prevalent use of any ADHD medication. Of the secondary outcomes, prevalent use of any ADHD medication was associated with a statistically significant 0.43-fold (95% CI: 0.24–0.79) hazard of nonaccidental death (Table 3). The other HRs for all-cause, nonaccidental, and nonsuicide death were numerically less than 1, although corresponding 95% CIs included 1 (Table 3).

TABLE 3 Prevalent ADHD Medication Users Versus Nonusers and the Rate of Validated Cardiovascular Events and of Death Events

Exposure	No. of Validated Events in ADHD Medication Users	Crude Incidence Rate per 10 000 Person-Years in ADHD Medication Users (95% CI)	No. of Validated Events in Non-ADHD Medication Users	Crude Incidence Rate per 10 000 Person-Years in Non-ADHD Medication Users (95% CI)	Data Source–Adjusted HR (95% CI)	Interaction by Data Source *P*
Sudden death or ventricular arrhythmia						
Amphetamines	0	0.00 (0.00–0.74)	[b]	0.13 (0.05–0.27)	Inestimable	—
Atomoxetine	[b]	1.90 (0.05–10.59)	0	0.00 (0.00–0.50)	Inestimable	—
Methylphenidate	[b]	0.11 (0.00–0.65)	[b]	0.07 (0.03–0.15)	1.30 (0.15–11.14)	.990
Any ADHD medication	[b]	0.10 (0.01–0.35)	11	0.06 (0.03–0.11)	1.43 (0.31–6.61)	.987
Stroke						
Amphetamines	0	0.00 (0.00–0.74)	[b]	0.11 (0.04–0.24)	Inestimable	—
Atomoxetine	0	0.00 (0.00–7.01)	0	0.00 (0.00–0.50)	Inestimable	—
Methylphenidate	0	0.00 (0.00–0.43)	[b]	0.06 (0.02–0.14)	Inestimable	—
Any ADHD medication	[b]	0.05 (0.00–0.27)	12	0.07 (0.04–0.12)	0.89 (0.11–7.11)	.988
MI						
Amphetamines	0	0.00 (0.00–0.74)	[b]	0.06 (0.01–0.16)	Inestimable	—
Atomoxetine	0	0.00 (0.00–7.01)	0	0.00 (0.00–0.50)	Inestimable	—
Methylphenidate	0	0.00 (0.00–0.43)	[b]	0.01 (0.00–0.06)	Inestimable	—
Any ADHD medication	0	0.00 (0.00–0.18)	[b]	0.02 (0.01–0.06)	Inestimable	—
Composite end point of stroke or MI						
Amphetamines	0	0.00 (0.00–0.74)	[b]	0.15 (0.06–0.29)	Inestimable	—
Atomoxetine	0	0.00 (0.00–7.01)	0	0.00 (0.00–0.50)	Inestimable	—
Methylphenidate	0	0.00 (0.00–0.43)	[b]	0.07 (0.03–0.15)	Inestimable	—
Any ADHD medication	[b]	0.05 (0.00–0.27)	16	0.09 (0.05–0.15)	0.72 (0.09–5.57)	.986
All-cause death						
Amphetamines	[a]	2.01 (0.97–3.70)	160	2.96 (2.52–3.46)	0.92 (0.48–1.76)	<.001
Atomoxetine	0	0.00 (0.00–7.01)	[a]	1.23 (0.56–2.33)	Inestimable	—
Methylphenidate	17	1.98 (1.15–3.17)	268	2.87 (2.54–3.23)	0.79 (0.48–1.29)	.634
Any ADHD medication	40	1.94 (1.39–2.64)	495	2.83 (2.59–3.09)	0.77 (0.56–1.07)	.006
Nonaccidental death[b]						
Amphetamines	[a]	0.42 (0.05–1.50)	19	1.28 (0.77–2.01)	0.27 (0.06–1.18)	1.000
Atomoxetine	0	0.00 (0.00–7.08)	0	0.00 (0.00–2.14)	Inestimable	—
Methylphenidate	[a]	0.96 (0.42–1.90)	35	1.37 (0.96–1.91)	0.64 (0.29–1.40)	1.000
Any ADHD medication	13	0.66 (0.35–1.12)	77	1.32 (1.04–1.65)	0.43 (0.24–0.79)	1.000
Nonsuicide death[b]						
Amphetamines	[a]	1.87 (0.86–3.55)	25	1.69 (1.09–2.49)	0.97 (0.45–2.11)	1.000
Atomoxetine	0	0.00 (0.00–7.08)	0	0.00 (0.00–2.14)	Inestimable	—
Methylphenidate	13	1.56 (0.83–2.67)	54	2.12 (1.59–2.76)	0.65 (0.35–1.20)	1.000
Any ADHD medication	30	1.52 (1.02–2.16)	113	1.93 (1.59–2.32)	0.66 (0.44–1.00)	1.000

[a] Omitted per Centers for Medicare and Medicaid Services Privacy Guideline policy.

[b] These analyses were performed using proportional hazard regression conditioned on the matching variables.

Claims-Based Events in Incident Users and Prevalent Users (Secondary Outcome)

As noted above, the low PPVs (41%–50%) of the claims-based cardiovascular events in children and adolescents led us to conclude that results on the basis of these outcomes are unreliable in this age group. Nevertheless, for the sake of completeness and transparency, we present them briefly here. In the analyses of all claims-identified cardiovascular events in incident users, none of the HRs differed from 1 in the combined data set and ranged from 0.80 to 1.66 (data not shown, but available on request). In the analyses of prevalent users, none of the HRs was statistically elevated (data not shown, but available on request), with the exception of the associations between a claims-based principal diagnosis of sudden death or ventricular arrhythmia and use of atomoxetine (HR: 10.66 [95% CI: 1.68–67.52]), methylphenidate (HR: 2.54 [95% CI: 1.33–4.85]), and any ADHD medication (HR: 1.92 [95% CI: 1.22–3.01]).

DISCUSSION

In this very large cohort study conducted in 2 distinct populations, we found that the incidence of validated sudden death or ventricular arrhythmia, stroke, and MI was very low. In analyses of validated events, many of the HRs were inestimable because of low numbers of events, and those that were estimable had very wide 95% CIs. Thus, although the low incidence of events does not permit us to exclude the existence of moderate or even large relative associations, the absolute risk of cardiovascular events in children and adolescents receiving ADHD medications in this very large cohort was still very low. Also arguing against an important increase in risk is the observation that neither all-cause death, nonaccidental death, nor nonsuicide death was more common in those receiving ADHD medications than unexposed subjects. In addition, baseline cardiovascular diagnoses and risk factors seemed to be more prevalent in the treated than the control group.

From a methodologic perspective, a low PPV is understandable, given that PPV is directly proportional to incidence in the population studied, and the incidence of cardiovascular events in children and adolescents is very low. If the PPVs were lower in the exposed than unexposed subjects, it might suggest that exposure may have made it more likely that diagnostic codes for cardiovascular events appeared incorrectly on the discharge record, which could artificially inflate the rate of (unvalidated) events in the exposed group. However, there was an insufficient number of validated events to make a definitive conclusion about differential PPVs. For example, the PPV of ventricular arrhythmia or sudden death was 33% (95% CI: 11–62) in users and 42% (95% CI: 30–55) in nonusers. Although these numbers are somewhat different, both are too low to rely on, and there is considerable overlap in their 95% CIs. Such ascertainment bias might have been responsible for the few associations observed in the secondary analyses of claims-based cardiovascular events.

The low rate of validated sudden death or ventricular arrhythmia found in this study is lower than the rate found in an earlier study. In particular, Wren et al[23] found an incidence rate of sudden death of 0.33 per 10 000 per year in those aged 1 to 20 years. If we assume that the PPV in the unavailable records in our study was the same as those for whom records were obtained, the incidence rate of sudden death or ventricular arrhythmia in our study would have been 0.21 to 0.28 per 10 000 per person-years in nonusers, which is very similar to these previous findings. Our incidence rate of all-cause death is squarely within the range of the rate of all-cause death in the United States, which ranges from 1.37 to 6.19 per 10 000 subjects aged 5 to 19 years.[24]

Three previous studies have tried to evaluate the rate of cardiovascular events in children and adolescents. In 2 smaller studies, no sudden cardiac death events were found among 32 807 and 5351 stimulant users.[5,7] Nonetheless, in 1 of these 2 studies, stimulant users had a 1.20-fold (95% CI: 1.04–1.38) hazard for emergency-department visits for an outcome that included less severe cardiac events and symptoms than we studied (eg, angina, hypertensive disease, syncope, and palpitations) compared with unexposed patients with ADHD.[5] A higher degree of clinical vigilance for cardiac events in the treated groups might explain this very weak association. In the third study, a case-control study using US mortality data, subjects aged 7 to 19 years who died suddenly had a 7.4-fold (95% CI: 1.4–74.9) odds of having used stimulants compared with those who died in a motor-vehicle crash.[6] However, given the small number of stimulant-exposed case ($n = 10$) and control ($n = 2$) subjects, a delay of 1 to 23 years between time of death and collection of data, possible recall bias for stimulant use, and possible higher likelihood of postmortem inquiries into the cause of death in those who died suddenly compared with those who died in a car crash, its results may have been biased away from the null.

An important strength of this study is our very large and diverse study population. Another strength is the validation of our study outcomes. We assessed the validity of study events rather than relying on claims-based diagnoses, which we found to be unreliable. An additional strength is inclu-

sion of all-cause death, which should be recorded completely and nondifferentially.

One limitation of our study is the low retrieval rate of medical records, which reduced our power to detect associations with validated events. However, the retrieval rate was very similar in unexposed and exposed groups, which should not have caused a bias toward the null. Furthermore, the low retrieval rate did not affect our analyses of death outcomes, which were also consistent with no increased cardiovascular risk. Another limitation is the potential for residual confounding. Because of the small number of events, we were unable to adjust simultaneously for multiple potential confounding factors. In addition, not all factors that one would like to evaluate as potential confounders are recorded in administrative data, including baseline blood pressure and BMI. Also, patients may have undiagnosed diseases (eg, congenital heart disease). In addition, there is underreporting of diagnoses of psychiatric conditions (eg, ADHD) in administrative databases, which most likely resulted in lower frequency of these diagnoses of psychiatric conditions than expected a priori.

CONCLUSIONS

We found low rates of validated severe cardiovascular events and of all-cause, nonsuicide, and nonaccidental death in children and adolescents receiving ADHD medications. Our results do not suggest the existence of a difference in risk between ADHD medication exposed and unexposed subjects.

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(Continued from first page)

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