Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
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Subject:	FDA / AHRQ-sponsored observational studies of cardiovascular events with drugs for Attention Deficit Hyperactivity Disorder (ADHD)
Drug Name(s):	Amphetamine products, methylphenidate products, atomoxetine
Tracked Safety Issue Number:	TSI #114
Applicant/sponsor:	multiple
OSE RCM #:	2006-536

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EXECUTIVE SUMMARY

Among drugs used for attention-deficit hyperactivity disorder, blood pressure and heart rate increases have been observed in patients treated with the sympathomimetics methylphenidate and amphetamine, and with atomoxetine. In view of these cardiovascular pharmacologic effects, plus spontaneous postmarketing reports of serious cardiovascular events with use of ADHD drugs, FDA, in partnership with the Agency for Healthcare Research and Quality (AHRQ), sponsored observational studies of serious cardiovascular events with drugs for ADHD. The project was divided into three separate but related studies. One study assessed myocardial infarction (MI), stroke, and sudden cardiac death (SCD) with use of ADHD drugs by children and young adults aged 2-24 years; a second study assessed MI and SCD among non-elderly adult users (aged 25-64 years), and the third study evaluated stroke in non-elderly adult users. The third study also included an analysis of the composite endpoint (SCD plus MI plus stroke) in adults.

These studies were retrospective cohort studies using health care claims databases from several sources: Kaiser Permanente, Tennessee Medicaid, Washington State Medicaid, Ingenix, and HMO Research Network. Drug exposures were identified from prescription claims data. Outcomes of stroke, MI, or SCD were identified from diagnoses in claims data, and from searches of vital statistics and death certificate data. Potential cases were either adjudicated from medical records by experts blind to exposure status, or were identified using electronic data case definition algorithms.

The youth study included 373,667 person-years of ADHD drug exposure, during which there were 7 serious cardiovascular events (4 strokes and 3 sudden deaths). All 7 occurred in Medicaid patients, although Medicaid patients contributed only about half of the total exposed person time. In comparison to nonuse, there was no association of such events with ADHD drug use (adjusted hazard ratio 0.75, 95% confidence limits 0.31-1.85). Additional analyses including use of a former user reference group did not materially affect the finding of no association with drug exposure. The inferential value of not finding an association is tempered by the fact that there were only seven serious cardiovascular events during ADHD drug exposure, indicating a low absolute risk, but limiting the ability to make comparisons. The results are inconsistent with the highly elevated risk reported in the literature, such as the 7-fold increase in sudden death reported by Gould et al., but a more modest increase in risk cannot be excluded.

In the adult sample, for the composite outcome of stroke plus MI plus SCD, there were a total of 107,322 person years of ADHD drug exposure and 234 events, a much higher rate than in the youth sample, as expected. In comparison to nonuse, current use of ADHD drugs in the adult sample was associated with a statistically significant lower risk of serious cardiovascular events (adjusted incidence rate ratio 0.80, 95% confidence limits 0.69-0.92). Although remote users of

ADHD drugs had the highest unadjusted incidence of these events, with adjustment, remote users had a statistically significant lower risk of serious cardiovascular events compared to non users (adjusted incident rate ratio 0.76, 95% confidence limits 0.66-0.87). However, with remote users as the reference group, the adjusted incidence rate ratio for the composite outcome is 1.05 (95% confidence limits 0.87-1.26).

A true cardiovascular protective effect persisting after drug use in adults, as suggested by the main analysis, seems implausible. Rather, this result suggests, speculatively, a potential "healthy user" bias encountered in some observational studies when patients who sought treatment tended to be healthier or have a more health conscious behavior than non-users. This is evidenced by the fact that when remote users are used as the reference group, the adjusted relative risks were closer to one suggesting that the users population might be inherently different from the nonuser comparison group. However, with an upper confidence limit for the rate ratio of 1.26, those results allow for the possibility of a moderate increase cardiovascular risk.

In terms of next steps, while the results make a several-fold elevation in risk unlikely, given the above-noted caveats, no labeling changes seem warranted. The feasibility of a randomized controlled trial meta-analysis for cardiovascular events in the adult population should be explored. There are a growing number of adult clinical trial development programs for ADHD, and serious cardiovascular events are not as rare among adults as they are in pediatric clinical trials.

1 BACKGROUND/HISTORY

Medications approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) include several sympathomimetics, atomoxetine, clonidine and guanfacine. Of these, blood pressure and heart rate increases have been observed in patients treated with the sympathomimetics methylphenidate[1] and amphetamine,[2] and with atomoxetine.[3] Since increased cardiovascular mortality has been linked both to increased heart rate[4] and to increased blood pressure,[5] there is some rationale for the hypothesis that such pharmacologic effects may confer increased cardiovascular risks to treated patients.

Several other lines of evidence also lend plausibility to this hypothesis. Postmarketing surveillance data has disclosed a number of case reports of pediatric sudden deaths with ADHD drug treatment, although the number of such reports per se does not clearly indicate an association.[6] A case-control study of the sympathomimetic phenylpropanolamine for appetite suppression found an association with hemorrhagic stroke; while the odds ratio was approximately 16, because of the infrequency of hemorrhagic strokes, the number needed to harm was estimated at more than 100,000.[7] A more recent example is sibutramine, a norepinephrine and serotonin reuptake inhibitor associated with increased heart rate and blood pressure, and which had been marketed for obesity management. A multi-year placebo-controlled study in patients with cardiovascular risk factors (the "SCOUT" study) showed that sibutramine conveyed a 28% increase in nonfatal myocardial infarctions (MI) and a 36% increase in nonfatal strokes.[8]

The topic of cardiovascular risks from ADHD drugs was discussed at a February 2006 meeting of the FDA Drug Safety and Risk Management Advisory Committee.[9] The Advisory Committee discussed the conduct of an observational study to address this issue. Subsequently, FDA and the Agency for Healthcare Research and Quality (AHRQ) co-sponsored the observational studies which are the subject of this review. This reviewer served as the FDA representative on the Steering Committee for these studies. The complete roster of the Steering Committee is shown below.

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Grateful acknowledgement is made by this reviewer, who served as the FDA representative on the Steering Committee, to the other FDA members of the study team: From the Office of Surveillance and Epidemiology, Drs. David Graham, Kate Gelperin, and Judy Staffa; from the Division of Psychiatry Products, Drs. Lourdes Villalba and Mark Ritter; and from the Office of Biometrics, Drs. Bradley McEvoy and LaRee Tracy.

Formal work on the studies began in September 2006 with drafting of the protocols. The studies received Institutional Review Board (IRB) authorization from the relevant local IRBs and from the FDA Research in Human Subjects Committee. Phase I of the studies involved the enumeration of drug exposures and candidate numbers of events from each site's claims databases, and Phase II involved adjudication of events using medical records and statistical analyses.

Several observational studies have already been undertaken to assess the cardiovascular risks of ADHD medications. The National Electronic Injury Surveillance System/Cooperative Adverse Drug Event Surveillance study of ER visits for events associated with stimulants, from August 1, 2003, to December 31, 2005, estimated that out of 188 total visits related to stimulants, 14% were for cardiovascular complaints.[10] A study using Florida Medicaid data on patients 3-20 years old treated with stimulants found no sudden cardiac deaths in 43,000 person-years of exposure to stimulants, but did find an increase in cardiac-related emergency department visits among current stimulant users compared to nonusers.[11] Another study, using the General Practice Research Database in the United Kingdom, found no sudden deaths in a total of 18,637 person-years of exposure to methylphenidate, dexamphetamine and atomoxetine.[12] However, a case-control study of 564 pediatric sudden deaths among children and adolescents aged 7-19 years without obvious heart disease,[13] found that ten of the sudden death cases had been receiving a stimulant, compared to only 2 individuals from a comparison group of motor vehicle accident victims. This yielded an adjusted odds ratio of 7.4 (with 95% confidence limits of 1.4-74.9). Although the association was statistically significant, limitations of this study included relatively few exposed cases, and the possibility that ascertainment of stimulant use was biased if it was not investigated as rigorously for a motor vehicle accident victim compared to a sudden death victim. A claims-based study of cerebrovascular outcomes among 42,993 adult atomoxetine and stimulant users found an elevated risk of transient ischemic attacks (but not completed strokes) compared to a nonuser population.[14] Most recently, a study of 241,417 patients aged 3-17 years treated with amphetamine, methylphenidate or atomoxetine found no strokes or myocardial infarctions among treated

patients (although the authors did not disclose how much exposure time was represented in their sample). For sudden death, there was no association versus untreated children, but the width of the confidence limits indicates that the power of the study was limited (hazard ratio for sudden death or ventricular arrhythmia = 1.6, 95% confidence limits 0.2 - 13.6).[15] In addition, an unpublished study in adults by the same researchers at the University of Pennsylvania was presented at the International Conference on Pharmacoepidemiology in August 2011.[16] Briefly, this retrospective cohort study analyzed data from both Medicaid and private health insurance databases. New users of ADHD medications were matched to controls in a 4:1 ratio, yielding a total of 35,586 amphetamine users, 20,995 atomoxetine users, 43,999 methylphenidate users, and 415,406 nonuser controls. Among the cardiovascular outcomes studied, the positive finding was an association of methylphenidate (but not the other two compounds) with sudden death/ventricular arrhythmia (adjusted hazard ratio = 2.1, 95% c.i. 1.5-2.9). Also, the association was stronger at lower doses of methylphenidate (i.e., an inverse dose relationship), suggesting an influence of patient selection.

2 REVIEW METHODS AND MATERIALS

The primary materials reviewed are the following three completed study reports.

- Attention Deficit Hyperactivity Disorder Medications and Risk of Serious Cardiovascular Disease in Children and Youth. Adverse Effects of Psychostimulant Medications Working Group, April 29, 2011
    - Revised results tables received 8-11-11

- ADHD Medications and Risk of Serious Coronary Heart Disease In Young and Middle-Aged Adults. Adverse Effects of Psychostimulant Medications Working Group, April 29, 2011.

- ADHD Medications and Risk of Stroke In Young and Middle-Aged Adults. Adverse Effects of Psychostimulant Medications Working Group, July 22, 2011.

Secondary sources were the slides from Dr. William Cooper's presentation to the Drug Safety Board on March 17, 2011, various supplementary information sent separately from study reports, and the protocols for the two studies, dated 10-28-09 for the youth study and 9-18-2008 for the adult study. The adult stroke outcome, which is the subject of the third study report, was added as a protocol change (Appendix 7) to the adult protocol.

3 RESULTS OF REVIEW

3.1 ATTENTION DEFICIT HYPERACTIVITY DISORDER MEDICATIONS AND RISK OF SERIOUS CARDIOVASCULAR DISEASE IN CHILDREN AND YOUTH

3.2 PROPOSED OBJECTIVES/ACTUAL OBJECTIVES

3.2.1 Proposed/Actual Objective

The objective of this study was to evaluate the association of ADHD medications and serious cardiovascular disease, defined as acute myocardial infarction (AMI), stroke, or sudden cardiac death (SCD), in patients aged 2-24 years.

3.2.2 OSE Comments on Proposed/Actual Objectives

This is a clinically relevant, appropriate objective.

3.3 PROPOSED DESIGN/ACTUAL DESIGN

3.3.1 Proposed/Actual Design

This was a retrospective cohort study employing health care claims data. Exposure to ADHD medications was determined from pharmacy dispensing records, with the index date t0 taken as the date of the first prescription. The incidence of serious cardiovascular events of AMI, stroke, or SCD was determined from electronic health care claims data and verified by chart review where possible. The main comparison for the incidence of events was between patients using an ADHD drug and patients who did not use any ADHD medications during the study. Controls were obtained by sampling at random from the dataset at the date t0 corresponding to the first prescription for each medication user; controls were individuals with no ADHD medication use (nonusers) on or before date t0 and were selected in a 2:1 ratio, with matching on year of birth and gender. The end of follow-up time for both users and nonusers was when subject eligibility was lost (see below) or in the case of users, when the last prescription ended. A Cox proportional hazards method was used, so that the basic unit of analysis was person-time rather than patients. Note that individuals may have contributed person-time as non-users prior to becoming users. A secondary comparison was made between current users and individuals who had used an ADHD drug in the past. Propensity scores were calculated by site to define the probability of being an ADHD drug user on the first day of study follow-up, and were not recalculated even if user status later changed. Propensity scores were covariates in the analysis but were not used to match users to nonuser comparison patients; nor were any subjects excluded because of non-overlap in the propensity score distributions between users and nonusers.

3.3.2 OSE Comments on Proposed/Actual Design

The study design was efficient from the standpoint of including all eligible exposed person-time in the user cohort, thus ensuring the largest possible sample of person-time. The ideal comparison group would have been individuals with ADHD who were not medicated, but identifying a sufficient sample of such individuals in claims data would be challenging. Making the primary comparison between users and nonusers provides good sample size but is problematic, because those groups are likely to represent different clinical populations and it is unclear whether the adjustment tools (including propensity score adjustments) are sufficient to account for this. The opinion of the FDA team had been that a primary comparison between users and former users would be more valid; this analysis was included as a secondary analysis. Application of the propensity score method when large numbers of the nonuser group never had a clinical indication for the study drugs at all may be questioned. The decision not to trim the samples based on poor overlap in the range of propensity scores yielded a larger sample size, albeit with a probability of including clinically dissimilar patients. No sensitivity analysis employing trimming was conducted.

3.4 INFORMED CONSENT

3.4.1 Proposed/Actual Informed Consent (if any)

Not applicable.

3.4.2 OSE Comments on Proposed/Actual Informed Consent (if any)

None. Note that these studies were exempted from review by FDA's Research in Human Subjects Committee (see exemption letter RIHSC #07-042D), because FDA received no identifiable patient information.

3.5 DATA SOURCE(S)

3.5.1 Data Source(s)

Four sites supplied data for this study:

- Tennessee State Medicaid
- Washington State Medicaid
- Kaiser Permanente California
- Ingenix i3

Although all sites provided electronic health care claims data, note that the type of health care delivery differs by site. The Tennessee and Washington sites provided exclusively Medicaid patient data; Kaiser Permanente provided data from a large health maintenance organization, and i3 includes data on private fee-for-service insurance patients. In addition, individual state vital statistics records and the National Death Index (NDI) of the Centers for Disease Control and Prevention were searched to identify possible cases.

3.5.2 OSE Comments on Proposed/Actual Data Sources

The use of four different sites was motivated by the desire to gain the largest sample size possible, even at the risk of introducing heterogeneity into the data by virtue of using multiple sources. It should be borne in mind that there are regional differences in the prevalence of diagnosed ADHD,[17] which might be an indicator of clinical heterogeneity by geographical region in the medicated ADHD population, and regional differences in diagnosis. The use of NDI records was appropriate because deaths may not always be accounted for in claims databases, especially out of hospital deaths.

3.6 STUDY TIME PERIOD(S)

3.6.1 Study Time Period(s)

The study time period varied by site, according to the characteristics of their respective databases, as shown below (adapted from Table 1 of the study report). Follow-up was truncated at 2005 to allow an adequate margin for ascertainment of any deaths occurring toward the end of the study period. A secondary analysis was performed including only those years common to all sites (2000-2005).

Tennessee Medicaid	Kaiser Permanente	Ingenix i3	Washington Medicaid	Total
1986-2005	1999-2005	1998-2005	2000-2005	1986-2005

3.6.2 OSE Comments on Proposed/Actual Study Time Period(s)

The study period was selected to maximize sample size, and allow for adequate follow-up time to account for individuals who died, and it is appropriate to address those particular goals. Note that

the prevalence of use of stimulant medications by youths increased during the time period covered by this study.[18,19] As with geographical differences, changes in prevalence might introduce some heterogeneity in the clinical population treated with ADHD medications over the course of the study period. The secondary analysis limited to six years of data common to all sites is a reasonable procedure, although the sample size will be smaller.

3.7 POPULATION

3.7.1 Population

Eligible individuals were aged 2-24 years, without serious illnesses considered to have a significant mortality risk, listed below.

> **Exclusion illnesses**: sickle cell disease, cystic fibrosis, cerebral palsy, cancer, HIV, organ transplant, liver failure, renal dialysis (except single inpatient episode), respiratory failure, metabolic diseases, aplastic anemia, congenital immune deficiencies, lethal chromosomal anomalies.

A discharge diagnosis of MI or stroke within the preceding year was also exclusionary.

3.7.2 OSE Comments on Proposed/Actual Population

The study population is appropriate for the objective of the study, but does not permit meaningful assessments of risk in particular patient population sub-groups which may be of clinical interest (e.g., children with repaired congenital heart defects).

3.8 EXPOSURE

3.8.1 Exposure

Pharmacy records were used to identify prescriptions dispensed for one of the following drugs.

Study drugs
methylphenidate
d-methylphenidate
dextroamphetamine
amphetamine
pemoline
atomoxetine

Different categories of exposure time following the dispensing of a prescription for a study drug were defined:

Use category	Definition
Current use	Days supplied for prescription
Indeterminate use	Days 1-89 after last day of days supplied
Former use	Days 90-364 after last day of days supplied
Remote use	Days 365+ after last day of days supplied

For both users and non-users, follow-up continued until the end of the study period, death, the day before a diagnosis of an exclusionary illness, the 24th birthday, or termination of pharmacy benefits. Individuals could contribute multiple periods and categories of person-time.

3.8.2 OSE Comments on Proposed/Actual Exposure

There are some analytic implications for having a design in which individuals may contribute at different times to both the exposed group and the comparison group, and to account for this, the analysis employed robust sandwich variance estimators. The study drugs were those approved for the indication of ADHD at the time the study was initiated. All have the pharmacologic property of increasing heart rate and blood pressure, so it is reasonable to pool the exposure data across drugs for the purpose of studying cardiovascular risks. It should be noted that since the study was initiated, some new ADHD drugs have been approved. Also, pemoline is no longer marketed in the U.S., so its cardiovascular safety profile is no longer clinically relevant per se. However, its contribution to the total exposure was relatively minor (see below).

3.9 DISEASE OUTCOME OF INTEREST

3.9.1 Disease Outcome of Interest

There were three primary outcomes: sudden cardiac death (SCD), acute myocardial infarction (AMI), and stroke.

SCD: All deaths in the cohorts were identified from either state death certificates (Tennessee, Washington, Kaiser) or the NDI. Additionally, the NDI was searched for deaths of young adult individuals (18-24 years) whose enrollment ceased, since they might have died out-of-state. Candidate cases of SCD were deaths with an underlying cause designated as one of the following (listings reproduced from the study report):

Cardiac cause of death (ICD-9 390-459, ICD-10 I00-I99)
Congenital anomaly (ICD-9 740-759, ICD-10 Q00-89)
Diabetes (ICD-9 250, ICD10-E10-E14)
Collapse (ICD-9 780.2, ICD-10 R55)
Sudden death, unknown cause (ICD-9 798.0-798.9, ICD-10 R96)
Respiratory arrest (ICD-9 799.1, ICD-10 R09.2)
Death from ill-defined condition (ICD-9 799.8, ICD-10 R98)
Unknown cause of death (ICD-9 799.9, ICD-10 R99)

Also included as candidate cases were hospital or emergency room primary discharge diagnoses from among the following:

Cardiac arrest (ICD-9 427.5)
Sudden death, unknown cause (ICD-9 798.0-798.9)
Respiratory arrest (ICD-9 799.1)
Cardiac arrest due to a procedure (ICD-9 997.1)

Medical records were obtained for candidate cases when possible and abstracted by study personnel. The definition of SCD applied was “sudden, pulseless condition or collapse consistent with a ventricular tachyarrhythmia occurring in a community setting;” SCD that was resuscitated was also considered an event. Two cardiologists (it was unspecified whether they were pediatric or adult cardiologists) from Vanderbilt, blinded to exposure category, reviewed the medical records and adjudicated the events. Nonarrythmia cardiac causes of death were to be excluded,

and the reason noted on the Final Case Status Form. If medical records could not be obtained a computer algorithm derived from the classification of events for which medical records were available was applied to determine the classification of the case.

AMI: Candidate cases of AMI were identified by the following diagnostic codes present either on death certificates or as hospital primary discharge diagnoses:

Acute myocardial infarction (ICD-9 410, ICD-10 I21, I22)
Intermediate coronary syndrome (ICD-9 411.1, ICD-10 I20.0)
Acute coronary occlusion (ICD-9 411.8, ICD-10 I24)
Old myocardial infarction (ICD-9 412, ICD-10 I25.2)
Angina pectoris (ICD-9 413, ICD-10 I20.1, I20.8, I20.9)
Coronary atherosclerosis (ICD-9 414.0, ICD-10 I25.0, I25.1)
Aneurysm of heart (ICD-9 414.1, ICD-10 I25.3, I25.4)
Other chronic ischemic heart disease (ICD-9 414.8, ICD-10 I25.5-I25.9)
Sequelae of myocardial infarction (ICD-9 429.7, ICD-10 I23)

The case definition for AMI was "an acute cardiac event meeting the international diagnostic criteria for myocardial infarction (a combination of clinical symptoms, diagnostic cardiac enzyme elevation, or electrocardiogram changes)" with hospitalization. Medical records for candidate cases were abstracted by study personnel, and two Vanderbilt cardiologists who were blind to exposure status reviewed the clinical information. As with SCD, a computer algorithm was applied to determine case status if medical records were not available.

Stroke: Potential strokes were identified by the following codes on death certificates or primary hospital discharge diagnoses:

Intracerebral hemorrhage (ICD-9 431, ICD-10 I61, I64)
Nontraumatic extradural hemorrhage (ICD-9 432.0 ICD-10 I62.1)
Unspecified intracranial hemorrhage (ICD-9 432.9, ICD-10 I62.0, I62.9)
Occlusion and stenosis of precerebral arteries (ICD-9 433, ICD-10 I65)
Occlusion of cerebral arteries (ICD-9 434, ICD-10 I63, I66)
Transient cerebral ischemia (ICD-9 435, ICD-10 G45.9)
Acute, but ill-defined, cerebrovascular disease (ICD-9 436, ICD-10 I67, I68)
Late effects of cerebrovascular disease (ICD-9 438, ICD-10 I69)
Hemiplegia (ICD-9 342, ICD-10 G81)
Other paralytic syndromes (ICD-9 344 (not 344.6), ICD-10 G83)

The case definition of stroke was "an acute neurological deficit of sudden onset that persisted more than 24 hours, corresponded (sic) to a vascular territory" and not explainable by trauma, infection, vasculitis, or hypotension. As with the other outcomes, available medical records were abstracted and two Vanderbilt neurologists (it was not specified if they were pediatric neurologists) blind to exposure status adjudicated the cases. A computer algorithm was applied to cases for which there were no medical records.

3.9.2 OSE Comments on Proposed/Actual Disease Outcome of Interest

The outcomes are relevant to the assessment of cardiovascular risks for drugs that raise pulse and blood pressure. A suitably thorough attempt was made to identify relevant cases from death records. The case adjudication process was strengthened by use of specialists, blind to exposure status, but few details were provided on how clinical judgment was to be applied to determine

case status in reviewing medical records. Excluding deaths judged due to underlying cardiac disease probably enhanced specificity for a potential drug relationship, but theoretically may have limited the assessment of risk in individuals with existing heart disease. However, a secondary analysis which included those cases excluded for significant underlying heart disease had similar results to the main analysis.

The FDA representatives on the study team had requested enumeration of all deaths, as a secondary measure, in addition to sudden cardiac deaths, but this request was not honored. Although it is reasonable to combine all three types of events (SCD, AMI, stroke) into a single endpoint, the events need to be analyzed separately as well since it is not necessarily true that all three would share the same relationship or lack of relationship with ADHD drug treatment.

3.10 SAMPLE SIZE

3.10.1 Sample Size

There was no a priori sample size specified. All eligible current use person-time from all four sites was to be included. The following table, provided by the investigators 4-11-2008, shows the projected statistical power based on the preliminary data on exposures and event counts.

Table 1. Detectable rate ratios by outcome, youth study

Outcome (N of verifiable events)	Detectable rate ratios for current use of stimulants versus none
Sudden Cardiac Death (n=244)	1.65
AMI (n=122)	1.98
Stroke (n=310)	1.57
SCD or AMI (n=361)	1.52
SCD, AMI, or Stroke (n=664)	1.38

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3.10.2 OSE Comments on Proposed/Actual Sample Size

The approach taken had the goal of maximizing the included exposure time for ADHD drug users, but due to the rarity of the verified outcome events, statistical power was still limited; see Section 3.11 below.

3.11 ANALYSES AND/OR STUDY RESULTS

3.11.1 Analyses and/or Study Results

The table below provides an overview of the patient sample (without regard to exposure status) and is adapted from the study report. Note that the mean age varied by site and ranged from 9 to 12 years. Also, samples from two sites were entirely Medicaid patients.

Table 1. Overview of sample characteristics (all drug use categories combined).

Site	Tennessee Medicaid	Kaiser Permanente	Ingenix i3	Washington Medicaid	All
N in cohort	200,198	191,772	692,187	116,281	1,200,438
% Medicaid	100.0	4.4	0	100.0	27.0
Age in years, mean	8.7	11.1	12.0	10.0	11.1
First day of follow-up, mean	1999.0	2002.1	2002.3	2002.2	2001.7
Follow-up in years, mean	3.9	2.6	1.5	2.1	2.1

A total of 454 possible cases were identified, and medical records were available for review for 357 (79%) of these. On review, a total of 250 of the possible cases were deemed not to meet a case definition (e.g., syncope without an actual cardiac arrest), and an additional 30 were excluded as being due to extrinsic causes. Seven sudden deaths were excluded because the death was attributed to pre-existing heart disease. This left 77 cases meeting the definition for an endpoint. A computer algorithm was applied to the claims data for the 97 possible cases without medical records, and this identified an additional 8 cases meeting the definition for an endpoint. Thus, there were a total of 85 outcome events that were the subject of the analysis. Subsequently, the investigators discovered that four events counted as completed strokes were actually transient ischemic attacks, and these were deleted from revised results tables sent 8-11-11; three of these four were in nonusers and one in a non-current user.

The results for the comparison between current users and non-users are shown in the table below. The hazard ratios were calculated with Cox regression and used the following covariates:

- site-specific propensity score decile
- site
- medical conditions (serious cardiovascular disease, serious chronic illness)
- psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use)
- utilization variables (medical hospitalization and general medical care access)
- age
- calendar year

As shown, the estimated hazard ratio for all outcomes, current use versus non-use, was 0.75, with confidence limits including unity (0.31-1.85).

Table 2. Cardiovascular outcomes by use category and hazard ratios for current use/non-use

Outcome	Person-years	Events	Rate/100,000 person-years	Adjusted hazard ratio, Current User: Non-user (95% c.i.)
Sudden Cardiac Death				
Non-user	1,597,962	17	1.1	Reference
Non-current user*	607,475	13	2.1	1.52 (0.65-3.57)
Current User, any ADHD drug	373,667	3	0.8	0.88 (0.23-3.34)
Acute Myocardial Infarction				
Non-user	1,597,962	6	0.4	Not calculated
Non-current user*	607,475	3	0.5	Not calculated
Current User, any ADHD drug	373,667	0	0	Not calculated
Stroke				
Non-user	1,597,962	26	1.6	Reference
Non-current user*	607,475	9	1.5	0.80 (0.33-1.96)
Current User, any ADHD drug	373,667	4	1.1	0.93 (0.29-2.97)
Any of these three outcomes				
Non-user	1,597,962	49	3.07	Reference
Non-current user*	607,475	25	4.12	1.03 (0.57-1.89)
Current User, any ADHD drug	373,667	7	1.87	0.75 (0.31-1.85)

*includes indeterminate use, former use, and remote use

The next table, reproduced from the revised tables for the study report, shows a variety of secondary analyses and the issues they were intended to address. The estimated hazard ratios were all below one but with confidence limits including unity.

For current users, the numbers of events by specific drug were 4 for methylphenidate and one each for amphetamine, atomoxetine and pemoline. Three of the events during current use were SCDs and four were strokes; there were no AMIs during current use. The specific events by drug were not reported.

Table. Secondary analyses of cardiovascular events with ADHD drug use

Analysis	Limitation Addressed	Exposure	Reference	Hazard Ratio	95% Confidence Interval
Primary Analysis		Current	Non-user	0.75	0.31-1.85
Addressing Comparison Group					
Former Users as Reference	Unmeasured confounding	Current	Former	0.70	0.29-1.72
Addressing Exposure group definitions					
Restricted to New Users	Covariates measured at drug initiation	New	Non-user	0.73	0.24-2.10
Addressing Case definitions					
Include cases excluded for severe underlying cardiac disease (n=7)	Possible effect of underlying cardiac disease	Current	Non-user	0.71	0.29-1.72
Addressing age					
Stratified by age <18 years and age 18-24 years	Possible effect of age on risk	Current	Non-user	0.75	0.30-1.87

A description of the individual patients having events with current use is in the next table, derived from supplemental information supplied by the investigators (not appearing in the study report).

Table 3. Description of cardiovascular events during current use

Patient	Event	Event Description	Cumulative current use days
712898	Stroke	8 year old male, intraventricular hemorrhage and hydrocephalus, died on second hospital day.	334
4229226	Sudden death	22 year old male with autism, ADHD mental retardation. Sudden death. Autopsy showed dysplasia of AV node artery.	2490
4396143	Stroke	13 year old F, congenital heart disease, ADHD. Acute left middle cerebral artery infarct on imaging. ECHO - no thrombus.	419
2EEF4G293240	Sudden death	6 year old M, ADHD, sudden death, autopsy diagnosis cardiac arrhythmia and fibro-fatty change of the sino-atrial node	445
2KI7C9J75072	Stroke	18 year old, Down syndrome, ADHD (no congenital heart disease). Left middle cerebral artery infarct	314
HE2AM1C78012	Stroke	19 y.o. M with history of Williams syndrome, polycystic kidney disease. Acute infarct in the distribution of the left superior cerebellar artery.	1169
P8CC4C379080	Sudden death	14 year old F with ADHD; sudden death. Death certificate diagnosis cardiac arrhythmia, dilated cardiomyopathy.	347

There was considerable non-overlap in the propensity score distributions when examined with histogram, comparing current users to nonusers. However, there was no “trimming” of the sample to enhance overlap of the distributions, as is sometimes done; the investigators reported that adjustment using the Brenner method[20] showed good comparability between non-users and users (data not shown).

There was a discrepancy in the numbers of events by site, seen more clearly when Medicaid and non-Medicaid sites are pooled. The following table, adapted from a table prepared by Dr. David Graham, shows the events by this subgrouping; the differences in unadjusted rates are statistically significant. Note that this table is based on the original study report and includes four transient ischemic attacks that were subsequently removed from the denominators for stroke (3 from nonusers and 1 from noncurrent users); however, we did not receive information on whether these were in Medicaid or non-Medicaid patients.

Table 4. Events observed by Medicaid versus non-Medicaid sites

Sample		All	Nonuser	Noncurrent	Current
Medicaid	Patient-years	1,016,435	616,601	280,205	119,629
	Strokes	25	16	5	4
	AMI	5	3	2	0
	SCD	25	12	10	3
	Total	55	31	17	7
	Total events/100,000 pyrs	5.4	5.0	6.1	5.9
Non-Medicaid	Patient-years	1,562,669	981,361	327,269	254,037
	Stroke	18	13	5	0
	AMI	4	3	1	0
	SCD	8	5	3	0
	Total	30	21	9	0
	Total events/100,000 pyrs	1.9	2.1	2.8	0.0

With 95% confidence limits, the observed incidence rates per 100,000 person-years for total outcomes are 5.9 (2.4-12.1) in the Medicaid sample, and 0 (0-1.5) in the non-Medicaid sample (p-value = 0.0007, aStat statistical calculator application). For SCD alone, the corresponding incidence rates are 2.5 (0.5-7.3) for Medicaid and 0 (0-1.5) for non-Medicaid. By drug use category, the rate of SCD in the Medicaid sample was 2.5 per 100,000 per year for current use, 1.9 per 100,000 per year for nonusers.

3.11.2 OSE Comments on Proposed/Actual Analyses and/or Study Results

This study found no association of serious cardiovascular events with use of ADHD medications in younger patients. Although the sample included 373,667 person-years of drug exposure, there were only 7 exposed events, 3 of them SCDs. The 3 SCDs represent an incidence rate of 0.8 per 100,000 per year of drug exposure, when Medicaid and non-Medicaid users are combined; however, all 3 SCDs were in Medicaid patients. For comparison, literature estimates of the incidence of sudden death in youths have ranged from 1.3 to 8.5 per 100,000 per year,[21] although those estimates did not necessarily exclude some of the conditions that were excluded in this study.

The results of this study are inconsistent with a several-fold increased risk of sudden death, such as had been suggested by the point estimate of 7.4 for the odds ratio in the Gould case-control study, but the methodologies were different and probably do not permit direct comparison. The null finding is consistent with the lack of association found in more recent studies (the above-mentioned GPRD and University of Pennsylvania cohort studies). However, this study was not capable of ruling out a smaller level of risk for cardiovascular events, particularly so because the overall risk estimates derive from aggregating Medicaid and non-Medicaid data. Although the Medicaid versus non-Medicaid stratification was done post-hoc, the discrepancy in the event rates revealed raises questions about the appropriateness of combining those data sets to give a single hazard ratio.

3.12 ADHD MEDICATIONS AND RISK OF SERIOUS CORONARY HEART DISEASE IN YOUNG AND MIDDLE-AGED ADULTS

3.13 PROPOSED OBJECTIVES/ACTUAL OBJECTIVES

3.13.1 Proposed/Actual Objective

The purpose of this study was to examine whether ADHD medications are associated with a risk of myocardial infarction (MI) and sudden cardiac death (SCD) in adults aged 25-64 years.

3.13.2 OSE Comments on Proposed/Actual Objectives

This is a highly clinically relevant question to examine. Note that a third cardiovascular outcome, completed stroke, will be assessed in the same population in a separate report.

3.14 PROPOSED DESIGN/ACTUAL DESIGN

3.14.1 Proposed/Actual Design

The design was similar to the child study already described. Patients meeting eligibility criteria had their time under observation classified as to whether they were users of ADHD medications or not; for each episode of use of an ADHD medication, as evidenced by a prescription, two periods of nonuse were randomly selected for comparison, by matching patients on gender and birth year. As with the child study, the same patients could contribute periods of person-time as users and as non-users of ADHD medications. One important difference from the youth study was that the primary analysis method was Poisson regression rather than Cox proportional hazard. Another important difference was that in order to account for potential confounders, a cardiovascular risk score (CRS) was determined for each patient, via regression modeling of cardiovascular events using a variety of clinical and demographic variables (other than ADHD drug exposure). The resulting CRS was then used as a covariate in the Poisson regression modeling of the association of the outcomes with ADHD medications. As with the youth study, the principle reference group was nonusers of ADHD medications.

3.14.2 OSE Comments on Proposed/Actual Design

The use of CRS has been criticized by some authors[22] and it seems fair to say that it is not as well accepted as the more widely used propensity score adjustment method. More problematic is the choice of a reference group; having the reference group be patients who do not use ADHD medications raises the possibility of there being important but unapparent differences in the two populations being compared. This sets up the possibility for a so-called “healthy user bias,” in which users of medication are generally healthier and perhaps more attentive to their health needs than nonusers[23] The FDA study team had consistently recommended a former-user comparison group, with the rationale that former users of ADHD medication would probably be more similar to current users than patients who never used such medications. This reference group was used in a secondary analysis, to be described below.

3.15 INFORMED CONSENT

3.15.1 Proposed/Actual Informed Consent (if any)

Not applicable.

3.15.2 OSE Comments on Proposed/Actual Informed Consent (if any)

None.

3.16 DATA SOURCE(S)

3.16.1 Data Source(s)

Five sources supplied data for this study; there was some overlap with the data sources for the youth study.

- Kaiser Permanente Northern California
- Kaiser Permanente Southern California
- Ingenix i3
- Tennessee Medicaid
- HMO Research Network
    - Group Health
    - Harvard Pilgrim
    - HealthPartners
    - KPCO
    - Fallon Community*
    - KP Mid-Atlantic*
    - KPNW*

    *Did not contribute data for SCD analysis

All sites provided electronic health care claims data, but as with the youth study, various types of health care delivery systems were represented, including health maintenance organizations, Medicaid, and private insurance. The type of delivery system differed by site. As with the youth study, the National Death Index and state vital statistics records also were used as supplemental data sources for fatal events. Also, it should be noted that three sites in the HMO Research Network provided only electronic data, for the MI analysis alone; because chart review was not feasible at these three sites, they were not used in the SCD analysis.

3.16.2 OSE Comments on Proposed/Actual Data Sources

It is appropriate to use as many data sources as possible in order to increase the sample size, but the trade-off is the introduction of heterogeneity by combining data originating in diverse health care delivery systems with differing patient populations. Since fatal events may not be captured in health care claims databases, it is appropriate to search for fatal events using the National Death Index and state mortality records. With respect to the three HMO Research Network sites that could not provide charts for review, it was appropriate to use data from those sites for the MI endpoint alone, since claims for MI should have sufficient reliability without chart review, whereas SCD would be a more problematic endpoint to ascertain from claims alone.

3.17 STUDY TIME PERIOD(S)

3.17.1 Study Time Period(s)

The study report did not specify the time periods, although it did state that the start date ranged from 1986 for Tennessee Medicaid to 2002 for Kaiser Permanente Southern California. In the final protocol for the study, the following information was provided; however, the reason for the discrepancy in the start date for Kaiser Southern California is not clear.

Table 5. Time period for Adult MI/SCD Study

Site	Begin Date	End Date
Tennessee Medicaid	1986	2005
Kaiser Northern California	1998	2005
Kaiser Southern California	2001	2005
United Health Care	1998	2005
HMO Research Network	1998	2005

3.17.2 OSE Comments on Proposed/Actual Study Time Period(s)

Similar to the youth study, the time frame spans a period during which there were increases in use of these medications in the adult population.[24] It should be borne in mind that as use in the adult population expanded, the characteristics of the adults receiving these drugs may have varied over time.

3.18 POPULATION

3.18.1 Population

Patients were eligible for inclusion if they were 25-64 years of age, with 12 months or more of enrollment (including pharmacy coverage). The following conditions were exclusionary if a diagnosis was recorded within one year prior to eligibility: "sickle cell disease, cancer diagnosis (other than non-melanoma skin cancer), HIV infection, organ transplant, liver failure or hepatic coma, end-stage renal disease, respiratory failure, or severe congestive heart failure." Most often, eligibility was ended if the patient received one of these diagnoses, except that an MI, SCD or stroke occurring along with severe congestive heart failure was still counted as an event. For every prescription for a study drug dispensed to an eligible patient, two nonuser comparison patients were randomly selected, matched on gender and birth year, from a time period prior to or simultaneous with the study drug exposure of interest (but not after it). Note that future users could appear in the nonuser comparison group. The main cohort of current users included both prevalent and new users, in order to enhance the sample size; a secondary analysis was limited to new users, defined as those with no prescriptions for study drugs within the year prior to cohort entry.

3.18.2 OSE Comments on Proposed/Actual Population

It is appropriate to end study eligibility at age 65 years, since the geriatric patient population receiving ADHD drugs may differ in clinical characteristics from younger adults, and health care delivery to that age group is more complex since all are eligible for Medicare. The fact that some patients may appear in both the exposed and the comparison group introduces some complexities into the analysis. The new user cohort has methodological advantages over analyzing a mixture of new and prevalent users (e.g., it avoids the problem of depletion of susceptibles).

3.19 EXPOSURE

3.19.1 Exposure

The study drugs were the same as those in the youth study: methylphenidate, dextroamphetamine, amphetamines, pemoline, and atomoxetine. These were all the drugs with an ADHD indication during the study period. Exposure categories were as follows and differed from the definitions in the youth study. Note that a non-user could switch to a current user, if still meeting eligibility criteria at the time of a first prescription.

Use category	Definition
Current use	Days supplied for prescription
Indeterminate use	Days 1-30 after last day of days supplied
Former use	Days 31-365 after last day of days supplied
Remote use	Days 366+ after last day of days supplied
Non-use	Days with no current or past prescription at any time

A secondary analysis examined new users, defined as patients with no use in the year prior to cohort entry. Another secondary analysis considered duration of exposure within the category of current use.

3.19.2 OSE Comments on Proposed/Actual Exposure

As noted previously, it is proper to combine these drugs for the assessment of cardiovascular effects, since all increase pulse and blood pressure. Since the Poisson regression method assumes a constant rate ratio, it is good practice to examine that assumption by subgrouping exposure according to the duration of use, as was done here.

3.20 DISEASE OUTCOME OF INTEREST

3.20.1 Disease Outcome of Interest

The primary outcomes were acute myocardial infarction (MI) requiring inpatient care, or sudden cardiac death (SCD). The outcome of completed stroke will be analyzed in a separate report. The following summarizes how candidate cases were identified from discharge diagnoses.

MI: Hospital discharge diagnosis ICD-9 410.x, or a death certificate diagnosis of ICD-9 410.x, or ICD-10 121.x or 122.x.

SCD: Death certificate diagnoses of

Any cardiac system cause of death (ICD-9 390-429, ICD-10 I01,I05-09, I11, I13, I20-I52)
Congenital cardiac anomaly (ICD-9 745-746, ICD-10 Q20-28)
Collapse (ICD-9 780.2, ICD-10 R55)
Sudden death, unknown cause (ICD-9 798.0-798.9, ICD-10 R96)
Respiratory arrest (ICD-9 799.1, ICD-10 R09.2)
Death from ill-defined condition (ICD-9 799.8, ICD-10 R98)
Unknown cause of death (ICD-9 799.9, ICD-10 R99)

Hospital or emergency room primary diagnoses of

cardiac arrest (ICD-9 427.5),
ventricular fibrillation, flutter or tachycardia (ICD-9 427.4x, 427.1);
cardiac arrest due to a procedure (ICD-9 997.1).

Hospital or emergency room diagnoses of the following plus a secondary diagnosis indicating heart disease (ICD-9 390.x – 429.x)

collapse (ICD-9 780.2),
sudden death, unknown cause (ICD-9 798.0-798.9), and
respiratory arrest (ICD-9 799.1),

Resuscitated cardiac arrests were identified among patients discharged alive with a diagnosis of cardiac arrest (ICD-9 427.5) either as their primary diagnosis or as a secondary diagnosis accompanied by ventricular fibrillation, flutter or tachycardia (ICD-9 427.4x, 427.1).

Charts, death certificates and autopsy reports were requested for all candidate SCD cases and for a sample of MI cases (representing 31% of potential MIs). A clinician blind to exposure status used these materials for case adjudication. For candidate SCD cases without charts, a published computer algorithm[25] was applied. The protocol did not supply details on how the cases were to be adjudicated. From the study report, it appears that possible SCD cases that were judged to be of cardiac cause, but non-arrhythmic in nature, were excluded.

3.20.2 OSE Comments on Proposed/Actual Disease Outcome of Interest

The outcomes are clinically relevant, and use of vital statistics data is essential for identifying out-of-hospital deaths. Details on the adjudication process were not provided. As with the youth study, the OSE study team had requested an enumeration of all cause mortality, but this request was not honored. Exclusion of 22 cases from the category of SCD events because the deaths were "non-arrhythmic" in nature was probably not appropriate; acute MI can be a valid cause of sudden cardiac death, but such cases were evidently excluded. However, these 22 cases would have represented only 7% of the total number of events (see below).

3.21 SAMPLE SIZE

3.21.1 Sample Size

As with the youth study, there was no a priori sample size targeted; all available exposed person-time that met eligibility criteria was analyzed, in order to maximize sample size. Please refer to section 3.32.1 below, under the description of the Adult Stroke study, for power projections involving the composite (MI, SCD, stroke) endpoint.

3.21.2 OSE Comments on Proposed/Actual Sample Size

Because cardiovascular events are much more frequent in the adult population, the sample of exposed person time included many more events than was the case for the youth study (see below).

3.22 ANALYSES AND/OR STUDY RESULTS

3.22.1 Analyses and/or Study Results

At baseline the sample included a total of 152,852 current users, and 293,749 non-users. The total of 107,383 person-years of current use equates to a mean exposure of 0.71 years. The following lists the contribution of individual drugs to the total of current use person time:

Drug	% of current use person-time
Methylphenidate	45%
Amphetamine	44%
Atomoxetine	8%
Pemoline	3%

The next table displays some of the salient patient characteristics, expressed as percentage of total person-time in each use category. Females formed the majority of each category. Remote users were older and had more conditions associated with cardiovascular risks, as indicated by higher CRS values. Although the earliest data collected were from the mid-1980's, the data were skewed towards more recent years.

Table 6. Characteristics of person-time by ADHD drug use category

	Current Use (107,383 pt-yrs)	**Indeterminate use (51,739 pt-yrs)**	**Former Use (46,163 pt-yrs)**	**Remote Use (67,688 pt-yrs)**	**Non-use (534,070 pt-yrs)**
Characteristic	**% of total pt-yrs**	**% of total pt-yrs**	**% of total pt-yrs**	**% of total pt-yrs**	**% of total pt-yrs**
Demographics					
Gender					
Male	45.8%	45.3%	46.0%	46.6%	45.7%
Female	54.2%	54.7%	54.0%	53.4%	54.3%
Age					
25-44	50.4%	54.3%	55.2%	47.7%	50.9%
45-64	49.6%	45.6%	44.8%	52.4%	49.2%
Site					
KPNC	13.1%	9.9%	10.6%	11.8%	12.5%
KPSC	5.3%	3.8%	4.1%	2.3%	4.3%
Tennessee Medicaid	8.2%	10.5%	16.3%	30.4%	15.0%
HMORN	22.2%	18.8%	15.5%	13.7%	20.9%
Ingenix/I3	51.1%	57.0%	53.5%	41.7%	47.3%
Year					
2004-2005	46.6%	44.8%	43.4%	44.2%	44.8%
1986-2003	53.5%	55.1%	56.6%	55.9%	55.2%
Selected medical conditions					
ADHD	35.0%	29.1%	20.9%	14.1%	0.1%
Hypertension at baseline	13.5%	13.5%	14.9%	15.3%	12.7%
Obesity	10.1%	9.3%	10.7%	16.7%	8.7%
Diabetes	7.1%	7.2%	8.5%	13.8%	7.9%
Stroke/TIA	1.9%	2.0%	2.7%	5.4%	1.9%

Hyperlipidemia	24.8%	24.7%	26.9%	36.5%	22.4%
Peripheral vascular disease	1.6%	1.6%	1.8%	3.5%	1.4%
Cardiovascular Risk Score (CRS)					
CRS deciles 1-5 (lower risk)	70.5%	70.8%	66.6%	57.8%	76.8%
CRS deciles 6-10 (higher risk)	29.6%	29.2%	33.4%	42.2%	23.2%

A total of 1375 possible MI cases were identified, and for a sample of 410 of these, medical records were requested for adjudication, with sufficient information obtained for 371. A total of 353 of the 371 were confirmed with adjudication. An additional 1004 events were confirmed by computer case definition alone, yielding a total of 1357 MI events for the analysis. For SCD, attempts were made to adjudicate all 411 possible cases; 139 were confirmed by chart review and 157 by computer algorithm, yielding a total of 296 SCD events for analysis. Of the 69 SCD cases that were ruled out by adjudication, 26 were judged non-cardiac deaths and 22 were judged cardiac deaths that were not arrhythmic in nature (see above under Disease Outcome of Interest).

The following tables, adapted from the study report, display the crude and adjusted results. The new users subgroup includes patients with no study drugs for a year prior to cohort entry. The first table shows the analysis for SCD plus MI events. The "Full Cohort" results may be considered the primary analysis for this study.

Table 7. MI and SCD outcomes.

Cohort/ subgroup	Person-yrs	Number of Events (MI or SCD)	Rate/1,000 person-yrs	Incidence rate ratio**	95% CI
Full cohort	807044.6	1582	1.96		
Current	107383.3	174	1.62	0.87	0.74 – 1.02
Former*	165590.8	367	2.22	0.87	0.78 – 0.99
Nonuser	534070.5	1041	1.95	1	reference
Pts with history of CVD^	237645	980	4.12		
Current	36616.7	112	3.06	0.87	0.71 – 1.07
Former*	59027.2	252	4.27	0.91	0.78 – 1.05
Nonuser	142001.1	616	4.34	1	Reference
New users only	487157.1	1082	2.22		
Current	52129.2	87	1.67	0.76	0.61 – 0.95
Former*	117124.9	285	2.43	0.83	0.73 – 0.96
Nonuser	317903	710	2.23	1	Reference

* Includes indeterminate, former and remote users

**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)

^ Cardiovascular disease (see study report for complete definition)

This table excludes the three HMORN sites that did not provide data on SCD endpoints.

The next table shows the results for the SCD outcome alone.

Table 8. SCD outcome results.

Cohort/ subgroup	Person-yrs	Number SCD Events	Rate/1,000 person-yrs	Incidence rate ratio**	95% CI
Full cohort	809220.6	296	0.37		
Current	107525	32	0.30	0.81	0.55 – 1.18
Former*	166180.1	84	0.51	0.91	0.70 – 1.18
Nonuser	535515.5	180	0.34	1	reference
Pts with history of CVD^	238847.9	194	0.81		
Current	36684.5	23	0.63	0.87	0.55 – 1.38
Former*	59396.2	62	1.04	0.99	0.72 – 1.35
Nonuser	142767.2	109	0.76	1	reference
New users only	488581.1	222	0.45		
Current	52203.2	15	0.29	0.63	0.37 – 1.08
Former*	117556.8	74	0.63	0.99	0.74 – 1.32
Nonuser	318821.1	133	0.42	1	reference

* Includes indeterminate, former and remote users

**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)

^ Cardiovascular disease

This table excludes the three HMORN sites that did not provide data on SCD endpoints.

The third table displays only the MI outcome results.

Table 9. MI outcomes.

Cohort/ subgroup	Person-yrs	Number AMI Events	Rate/1,000 person-yrs	Incidence rate ratio**	95% CI
Full cohort	844615.3	1357	1.61		
Current	113324.2	152	1.34	0.88	0.74 – 1.05
Former*	171548	298	1.74	0.87	0.76 – 0.99
Nonuser	559743.1	907	1.62	1	reference
Pts with history of CVD^	246935.4	828	3.35		
Current	38379.7	95	2.48	0.88	0.70 – 1.09
Former*	60687.4	200	3.30	0.89	0.76 – 1.05
Nonuser	147868.3	533	3.60	1	reference
New users only	510404.1	906	1.78		
Current	55533.9	77	1.39	0.80	0.63 – 1.02
Former*	121371.9	222	1.83	0.80	0.68 – 0.93
Nonuser	333498.3	607	1.82	1	reference

* Includes indeterminate, former and remote users

**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)

^ Cardiovascular disease

In every analysis shown above, current users had the lowest crude incidence rates among the three categories (current, former, and nonuser). This was reflected in adjusted incidence rate ratios (IRRs) having point estimates below unity; for former users, adjusted IRRs were also below unity. Focusing on MI or SCD alone yielded generally similar adjusted IRRs with wider confidence limits (consistent with fewer events for analysis). Incidence rates were higher among patients with a history of cardiovascular disease, as anticipated. In the new user adjusted analysis, both current use and former use were associated with a statistically significant lower risk of MI plus SCD, compared to nonuse.

A secondary analysis employed propensity score adjustment rather than the CRS adjustment; the results were generally consistent with the CRS-adjusted analysis. The propensity-score adjusted IRR for MI plus SCD in the new user cohort was 0.74 (95% c.i. 0.58 - 0.94), for current use versus nonusers as the reference.

Analysis of the new user cohort according to the duration of current use, with nonusers as the reference group, did not disclose any major differences in the adjusted IRRs with respect to duration of use; all crude incidence rates for the various categories of duration of use were lower than the crude incidence rate for nonusers of 1.95 events per 1000 person-years (data not shown).

Analysis of incidence rates by specific study drug did not disclose any major discrepancies in the incidence of events with use of specific drugs (data not shown).

With respect to heterogeneity by site, the Tennessee Medicaid site had the highest incidence of SCD and MI overall (regardless of exposure), and also had subjects with a greater baseline

prevalence of cardiovascular conditions in general. However, when IRRs were calculated by individual site (with a nonuser reference group), Tennessee Medicaid had the lowest IRRs of any site.

The following table shows the analysis recommended by the FDA study team, with remote users as the reference. The remote users had the highest event rate; however, after adjusting for variables including CRS, the adjusted IRR point estimates were close to or above one, consistent with the fact that remote users had a higher prevalence of risk factors as discussed previously.

Table 10. Combined outcome results, remote users as reference group

User status	Person-yrs	Number of MI or SCD Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted IRR**	95% CI
Current user	107383.3	174	1.62	0.59	0.48 – 0.73	1.04	0.85 - 1.29
Indeterminate user	51739.1	97	1.87	0.68	0.53 – 0.87	1.22	0.95 - 1.57
Former user	46163	84	1.82	0.66	0.51 – 0.86	0.99	0.76- 1.28
Remote user	67688.6	186	2.75	1	reference	1	reference

**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)

3.22.2 OSE Comments on Proposed/Actual Analyses and/or Study Results

In the primary analysis there was no observed increase in the incidence of MI or SCD with ADHD drugs; in a secondary analysis limited to new users, which could be considered a more refined and appropriate cohort for analysis,[26] there was actually a statistically significant decrease in the risk of such events with current and with former use of these drugs relative to no use. While these results are inconsistent with there being a several fold increased risk of MI or SCD, the finding of a cardioprotective effect which persists after use seems implausible, given the pharmacology of the drugs in question. Indeed, the magnitude of the apparent cardioprotective effect rivals that for aspirin, which a recent clinical trial meta-analysis found produced only a 10% reduction in major cardiovascular events among patients without CVD.[27] A more plausible explanation would be residual confounding that was not accounted for with the adjustment methods.

A "healthy user" type of bias, such as has been postulated for some observational studies, might have played a role. One strategy adopted to address the potential for unmeasured confounders was to use patients who had previously been on an ADHD drug (remote users) as the reference group. However, the remote user group had a generally higher prevalence of cardiovascular risk factors. Therefore, the point estimate for the unadjusted IRR (for current use: remote use) is below one and statistically significant, while the adjusted IRR point estimate is greater than one (but with a confidence limit that includes one).

Accordingly, while these results clearly do not support an association with MI or SCD, it is difficult to judge exactly what level of risk has been ruled out, since in the main analysis the adjusted IRRs appear to be biased towards a clinically implausible protective effect. Sibutramine has similar cardiovascular effects to the drugs in this study, and in a randomized clinical trial involving overweight patients with cardiovascular disease, the hazard ratios for cardiovascular outcomes were 1.16 for the composite outcome and 1.28 for nonfatal MI.[28] The confidence limits for the adjusted IRRs in this study would suggest risks of this magnitude have been excluded numerically; however, because of the aforementioned bias apparent in the results, it would not be prudent to form that interpretation.

3.23 ADHD MEDICATIONS AND RISK OF STROKE IN YOUNG AND MIDDLE-AGED ADULTS

3.24 PROPOSED OBJECTIVES/ACTUAL OBJECTIVES

3.24.1 Proposed/Actual Objective

The objective of this study was to examine whether ADHD drugs increase the risk of stroke in adults aged 25-64 years.

3.24.2 OSE Comments on Proposed/Actual Objectives

This is a clinically relevant and important objective.

3.25 PROPOSED DESIGN/ACTUAL DESIGN

3.25.1 Proposed/Actual Design

This study employed the same design as the adult MI/SCD study described above.

3.25.2 OSE Comments on Proposed/Actual Design

Please refer to the previous comments on study design.

3.26 INFORMED CONSENT

3.26.1 Proposed/Actual Informed Consent (if any)

Not applicable.

3.26.2 OSE Comments on Proposed/Actual Informed Consent (if any)

None.

3.27 DATA SOURCE(S)

3.27.1 Data Source(s)

The following sites provided data for the adult stroke study. All of these sites also participated in the adult MI/SCD study, although not every HMO Research Network site from that study participated in the stroke study.

- Kaiser Permanente Northern California
- Kaiser Permanente Southern California
- Ingenix i3
- Tennessee Medicaid
- HMO Research Network:
    - Group Health
    - Harvard Pilgrim
    - HealthPartners
    - Kaiser Permanente Colorado
    - Kaiser Permanente Northwest

3.27.2 OSE Comments on Proposed/Actual Data Sources

As noted previously, the data sources represent a mixture health care delivery systems (public insurance (i.e., Medicaid), private health insurance, and health maintenance organization). No further comments.

3.28 STUDY TIME PERIOD(S)

3.28.1 Study Time Period(s)

The time period was identical to the adult MI/SCD study; please see section 3.17.1 above. Follow-up ended in 2005 for all sites, to allow time for capture of deaths in vital statistics data.

3.28.2 OSE Comments on Proposed/Actual Study Time Period(s)

No further comments.

3.29 POPULATION

3.29.1 Population

Eligibility criteria were identical to those for the adult MI/SCD study. Please refer to section 3.18.1 above.

3.29.2 OSE Comments on Proposed/Actual Population

No further comments.

3.30 EXPOSURE

3.30.1 Exposure

The study medications were the same as in the adult MI/SCD and the youth study. Exposure categories were defined using the classification from the youth study rather than the adult MI/SCD study, as shown:

Different categories of exposure time following the dispensing of a prescription for a study drug were defined:

Use category	Definition
Current use	Days supplied for prescription
Indeterminate use	Days 1-89 after last day of days supplied
Former use	Days 90-364 after last day of days supplied
Remote use	Days 365+ after last day of days supplied

3.30.2 OSE Comments on Proposed/Actual Exposure

The reason for employing the usage categories from the youth study, rather than matching the adult MI/SCD analysis, was not stated.

Otherwise, no further comments on the definition of exposure.

3.31 DISEASE OUTCOME OF INTEREST

3.31.1 Disease Outcome of Interest

The outcome of interest was stroke, defined as "an acute neurologic deficit of sudden onset that persisted more than 24 hours, corresponded to a vascular territory, and was not explained by other causes…" Strokes were classified as ischemic or hemorrhagic, and strokes during a hospitalization were excluded. The following ICD 9/10 codes were used to identify candidate strokes from electronic data:

- ICD-9 430, ICD-10 I60 subarachnoid hemorrhage
- ICD-9 431, ICD-10 I61, I64 intracerebral hemorrhage
- ICD-9 432.0, ICD-10 I62.1 non-traumatic extradural hemorrhage
- ICD-9 432.1 subdural hemorrhage
- ICD-9 432.9, ICD-10 I62.0, I62.9 unspecified intracranial hemorrhage
- ICD-9 433.00-.01, 433.10-.11, 433.20-.21, 433.30-.31, ICD-10 I65 occlusion and stenosis of precerebral arteries
- ICD-9 434.00-.01, 434.10-.11, 434.90-.91, ICD-10 I63, I66 occlusion of cerebral arteries
- ICD-9 436, ICD-10 I67, I68 acute, but ill-defined, cerebrovascular disease

Medical records were sought for all candidate stroke events, and the events were adjudicated by a team of six neurologists blinded to exposure status. In the event that suitable medical records or autopsy reports were unavailable, an adjudication algorithm based solely on diagnostic codes was employed.

3.31.2 OSE Comments on Proposed/Actual Disease Outcome of Interest

Details regarding the adjudication criteria employed by the neurologists, or of the secondary adjudication process using only ICD 9/10 codes, were not provided in the study report. Accordingly, it is difficult to comment on the appropriateness of the adjudication process. As noted previously, the investigators did not honor the request from the FDA study team to include an enumeration of deaths from any cause.

3.32 SAMPLE SIZE

3.32.1 Sample Size

There was no a priori sample size established for this study.

Based on preliminary exposure data and crude counts of patients with ICD 9/10 codes of interest, obtained during Phase I of the study (but without unblinding the exposure data for patients with events), the following table (which appeared in the final protocol) displays the estimated power in terms of incident rate ratios:

Table 11. Estimated power for detection of incident rate ratios based on preliminary (Phase I) data

Projected number of events	Detectable incident rate ratio (current users versus nonusers)
Sudden Cardiac Death (n=149)	1.87
AMI (n=1357)	1.26
Stroke (n=1073)*	1.29
SCD or AMI (n=1499)	1.25
SCD, AMI, or Stroke (n=2520)*	1.19

3.32.2 OSE Comments on Proposed/Actual Sample Size

The projected power, in terms of ability to cap the incident rate ratio with an upper confidence limit, was reasonable. However, the interpretation of these estimates is governed by the extent of potential bias or residual confounding in the data as alluded to earlier in the review.

3.33 ANALYSES AND/OR STUDY RESULTS

3.33.1 Analyses and/or Study Results

The sample included 152,852 current users and 293,749 non-users at baseline. The following table summarizes the exposure by use category.

Table 12. Exposure by use category

Use Category	Person-years	Mean person-years per patient
Current	111,935	0.74
Indeterminate	53,328	0.35
Former	47,333	0.31
Remote	69,202	0.46
Non-use	553,459	1.89

The proportion of exposure contributed by each individual drug, shown below, was very similar to the adult MI/SCD study sample.

Drug	% of current use person-time
Methylphenidate	45%
Amphetamine	43%
Atomoxetine	7%
Pemoline	3%

The next table displays the patient characteristics according to the proportion of person-time contributed.

Table 13. Patient characteristics by use category, in percentages of person-time

	Current Use (111,936 pt-yrs)	Indeterminate use (53,328 pt-yrs)	Former Use (47,333 pt-yrs)	Remote Use (69,202 pt-yrs)	Non-use (533,459 pt-yrs)
Characteristic	**% of total pt-yrs**	**% of total pt-yrs**	**% of total pt-yrs**	**% of total pt-yrs**	**% of total pt-yrs**
Demographics					
Gender					
Male	45.8	45.3	46.0	46.7	45.8
Female	54.2	54.7	54.0	53.3	54.2
Age					
25-44	50.0	53.9	54.9	47.4	50.5
45-64	50.1	46.0	45.1	52.6	49.5
Site					
KPNC	12.6	9.7	10.3	11.6	12.1
KPSC	5.1	3.7	4.0	2.2	4.2
Tennessee Medicaid	7.9	10.2	16.0	29.8	14.5
HMORN	25.4	21.0	17.3	15.4	23.5
Ingenix/I3	49.1	55.4	52.2	40.9	45.7
Year					
2004-2005	46.5	44.8	43.5	44.4	44.8
1986-2003	53.5	55.1	56.7	55.5	55.2
Selected medical conditions					
ADHD at baseline	35.5	29.6	21.4	14.5	0.1
Hypertension at baseline	13.4	13.5	14.8	15.2	12.6
Obesity	10.3	9.5	10.9	16.9	8.8
Diabetes	7.1	7.2	8.4	13.7	7.9
Stroke/TIA	1.8	1.9	2.6	5.2	1.8
Hyperlipidemia	24.5	24.5	26.7	36.3	22.3
Peripheral vascular disease	1.6	1.5	1.8	3.5	1.4
Cardiovascular Risk Score (CRS)					
CRS deciles 1-5 (lower risk)	66.0	67.7	65.2	61.6	78.3
CRS deciles 6-10 (higher risk)	34.0	32.3	34.8	38.4	21.6

The sample overlapped considerably with, but was not identical to, the sample for the adult MI/SCD study. As was true in that study, remote users on average were older, had higher CRS scores, and a higher prevalence of many risk factors, including previous stroke or TIA. Data tended to be from the most recent years, as with the MI/SCD sample. Descriptive data for the new users cohort was not provided.

A total of 980 candidate events for strokes were found using hospital discharge diagnoses and death certificates. Information from medical records was obtained for adjudication on 911 of these cases. Of those 911, 451 were confirmed by adjudication and 281 were not confirmed. Cases that were not confirmed included, among others, carotid endarterectomies, TIAs, and strokes predating the study. For 248 cases there were either no medical records or insufficient information, and these cases were subjected to a diagnostic-code based algorithm; 124 of them were confirmed as strokes in that way and included in the numerators. This yielded a total of 575 strokes for the analysis.

Of the 575 strokes, 148 (26%) were hemorrhagic, and 415 (72%) were ischemic; presumably 12 were not classified. Two-thirds of the strokes (378 out of 575) occurred in patients with a history of cardiovascular disease.

The next table shows the incidence of strokes by user category for the full sample and selected subgroups, and the adjusted incidence rate ratios. It can be seen that all the point estimates for the adjusted incidence rate ratios were below one, but the confidence limits included one, except for the remote user group in the new user cohort.

Table 14. Incidence and adjusted incidence rate ratios for stroke

Cohort/ subgroup	Person-yrs	Number of Strokes	Rate/1,000 person-yrs	Incidence rate ratio**	95% CI
Full cohort					
Current	111935.5	63	0.56	0.77	0.58 - 1.02
Former*	169863.2	137	0.81	0.83	0.68 - 1.02
Nonuser	553458.5	375	0.68	1	reference
Pts with history of CVD^					
Current	37964.1	45	1.19	0.85	0.61 - 1.19
Former*	60298.1	101	1.68	0.89	0.70 - 1.13
Nonuser	146439.8	232	1.58	1	reference
New users only					
Current user	54569.3	41	0.75	0.79	0.56 - 1.12
Indeterminate	30657.1	20	0.65	0.71	0.45 - 1.13
Former user	34644.6	26	0.75	0.74	0.49 - 1.11
Remote user	54702.5	56	1.02	0.72	0.54 - 0.98
Nonuser	328754.2	262	0.80	1.00	reference

* Includes indeterminate, former and remote users

**Adjusted for site, age, sex, calendar year, stroke risk factors

^ Cardiovascular disease

Analysis according to specific ADHD medication, duration of treatment, or type of stroke did not yield any statistically significant rate ratios.
The next table highlights the outcome in the new user cohort, with the remote user reference group as recommended by the FDA study team. All of the confidence intervals include one, and the point estimates are closer to one.

Table 15. Stroke outcome in new users cohort, with remote user reference group

User status	Person-yrs	Number of MI or SCD Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted IRR**	95% CI
Current user	54569.3	41	0.75	0.73	0.49 - 1.10	1.09	0.73 - 1.65
Indeterminate user	30657.1	20	0.65	0.64	0.38 - 1.06	0.99	0.59 - 1.65
Former user	34644.6	26	0.75	0.73	0.46 - 1.17	1.02	0.64 - 1.63
Remote user	54702.5	56	1.02	1.00	reference	1.00	reference

By site, Tennessee Medicaid had the highest rate of stroke (1.8 per 1000 person-years) and Harvard Pilgrim the lowest (0.3 per 1000 person-years), for all exposure categories combined. Consistent with this observation, the Tennessee Medicaid sample tended to have the highest prevalence of risk factors, including previous stroke or TIA, hypertension, and hyperlipidemia (data not shown). An analysis of heterogeneity in relative risks by site showed that the highest point estimate for current use: nonuse came from the Tennessee Medicaid data, but the statistical power for the subgroup analysis by site was limited.

Finally, the study report included data on a composite outcome of stroke, MI, or SCD. The table below displays the results on this composite outcome for the new user cohort only. The crude incidence rate was highest in the remote user group (which as noted previously tended to have a higher prevalence of risk factors) and lowest in the current user group. With nonusers as the reference, current use was associated with a statistically significant lower risk of serious cardiovascular events (adjusted IRR 0.68, 95% c.i. 0.56-0.82).

The results for the total cohort were largely similar and also showed a reduced rate of events with current use versus nonuse (data not shown).

Table 16. Results for composite outcome of stroke, MI or SCD, new users only

Use Category (new users only)	Person-yrs	Number of Strokes, MIs or SCDs	Rate/ 1,000 person-yrs	Nonuser reference		Remote user reference	
				Incidence rate ratio**	95% CI	Incidence rate ratio**	95% CI
Current user	52094.6	125	2.40	0.68	0.56 - 0.82	0.94	0.75 - 1.18
Indeterminate user	29694.2	82	2.76	0.80	0.63 - 1.01	1.11	0.86 - 1.44
Former user	33774.3	97	2.87	0.74	0.60 - 0.91	1.03	0.80 - 1.31
Remote user	53450.1	197	3.69	0.72	0.61 - 0.84	1.00	reference
Nonuser	317514.4	957	3.01	1.00	reference	-	-

**Adjusted for site, age, sex, calendar year, stroke risk factors

Adjustment using propensity scores rather than stroke risk scores did not materially affect the results on the composite of stroke, MI or SCD (after adjustment, current users had a reduced incidence compared to nonusers with both methods).

3.33.2 OSE Comments on Proposed/Actual Analyses and/or Study Results

This study did not find an association between use of ADHD drugs and stroke in non-elderly adults. In the whole sample and also in the subgroup of patients with cardiovascular disease, current users had the lowest crude incidence rate of stroke, and with a nonuser group as the reference, an incidence rate ratio less than one which was not statistically significant. Remote users had the highest crude stroke incidence rate, but after adjustment had an incidence rate ratio below one versus nonusers, most likely reflecting the influence of adjusting for risk factors which were more prevalent among remote users. With remote users as the reference group, the incident rate ratio for current use was closer to one.

For the composite outcome, with nonusers as the reference group, current use of an ADHD drug was associated with a statistically significant lower risk of stroke, MI, or SCD, in the range of effects seen with low dose aspirin. This effect is also seen with remote use. When remote users serve as the reference, the incident rate ratios are close to one. This suggests that there was residual confounding in the comparison to nonusers, which resulted in an apparent cardioprotective effect, not observed when previous users were the reference group. Such an effect might represent a so-called “healthy user bias” as discussed above.

4 SUMMARY AND RECOMMENDATIONS

1. Youth study
    a. No association between use of drugs for ADHD and stroke, MI, or SCD was identified in children and youths.
    b. The lack of association was not analysis dependent, and was noted in a variety of secondary analyses.
    c. The inferential value of not finding an association is tempered by the fact that there were only seven serious cardiovascular events during ADHD drug exposure in the analysis. This indicates a low absolute risk, but limits the ability to make statistical comparisons between users and nonusers.
    d. The inferential value of the results is further tempered by the observation that all events during drug exposure happened in Medicaid patients. This is unlikely to be due to chance and raises questions about the advisability of aggregating Medicaid and non-Medicaid data in a single analysis.
    e. The results appear inconsistent with a many-fold increase in risk (e.g., as was suggested by the Gould et al. study finding an odds ratio above 7 for sudden death), but the design and comparison group are radically different from the Gould et al. case-control study. Nonetheless, the power was not sufficient to rule out a smaller increase in risk.
2. Adult study
    a. No association between use of drugs for ADHD and stroke, MI, or SCD was identified among non-elderly adults.

b. With a nonuser comparison group, both current users and previous users of an ADHD drug displayed a statistically significant lower risk of the rate of serious cardiovascular events.

c. A true cardiovascular protective effect, persisting after drug use, seems implausible. Rather, this result suggests perhaps similar to the "healthy user" bias seen in some observational studies.

d. When remote users are the reference group, the adjusted relative risks are closer to one. However, those results can only rule out a high level of risk and are not adequate to rule out a risk on the order of that observed with sibutramine, for example.

3. No further labeling changes for the study drugs regarding cardiovascular events are warranted based on these results.

4. Observational data on these events is difficult to interpret because of the rarity of serious cardiovascular events among younger patients, and because of difficulties accounting for bias and confounding in data for adults.

5. The feasibility of a randomized controlled trial meta-analysis for cardiovascular events in the adult population should be explored. There are a growing number of adult clinical trial development programs for ADHD, and serious cardiovascular events are not as rare among adults as they are in pediatric clinical trials. Also, such a meta-analysis might explore the apparent discrepancy between the FDA-AHRQ study finding no association with sudden death, and the University of Pennsylvania study finding an association between methylphenidate and sudden deaths/arrhythmias.

5 REFERENCES

[1] Adler LA, Orman C, Starr HL, Silber S, Palumbo J, Cooper K, Berwaerts J, Harrison DD.. Long-term safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: an open-label, dose-titration, 1-year study. J Clin Psychopharmacol. 2011;31(1):108-14.

[2] Wilens TE, Hammerness PG, Biederman J, Kwon A, Spencer TJ, Clark S, Scott M, Podolski A, Ditterline JW, Morris MC, Moore H. Blood pressure changes associated with medication treatment of adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2005;66(2):253-9

[3] Strattera prescribing information. Available at http://pi.lilly.com/us/strattera-pi.pdf

[4] Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. Am Heart J. 1987;113(6):1489-94.

[5] Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.

[6] Gelperin K. Cardiovascular risk with drug treatments of ADHD: Overview of available safety data in children. Available at http://www.fda.gov/ohrms/dockets/ac/06/slides/20064210s_12_Gelperin_Cardiovascular%20Risk_files/frame.htm

[7] Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, Morgenstern LB, Wilterdink JL, Horwitz RI. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med. 2000;343(25):1826-32.

[8] James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C, Sharma AM, Shepherd GM, Rode RA, Renz CL; SCOUT Investigators. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med. 2010;363(10):905-17.

[9] Transcript available at http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4202t1.pdf

[10] Cohen AL, Jhung MA, Budnitz DS. Stimulant medications and attention deficit-hyperactivity disorder. N Engl J Med. 2006;354(21):2294-5.

[11] Winterstein AG, Gerhard T, Shuster J, Johnson M, Zito JM, Saidi A. Cardiac safety of central nervous system stimulants in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics. 2007;120(6):e1494-501.

[12] McCarthy S, Cranswick N, Potts L, Taylor E, Wong IC. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: a retrospective cohort study of children, adolescents and young adults using the general practice research database. Drug Saf. 2009;32(11):1089-96.

[13] Gould MS, Walsh BT, Munfakh JL, Kleinman M, Duan N, Olfson M, Greenhill L, Cooper T. Sudden death and use of stimulant medications in youths. Am J Psychiatry. 2009;166(9):992-1001.

[14] Holick CN, Turnbull BR, Jones ME, Chaudhry S, Bangs ME, Seeger JD. Atomoxetine and cerebrovascular outcomes in adults. J Clin Psychopharmacol. 2009;29:453-60.

[15] Schelleman H, Bilker WB, Strom BL, Kimmel SE, Newcomb C, Guevara JP, Daniel GW, Cziraky MJ, Hennessy S. Cardiovascular Events and Death in Children Exposed and Unexposed to ADHD Agents. Pediatrics. 2011 May 16. [Epub ahead of print]

[16] Schelleman H, Bilker WB, Kimmel SE, Daniel GW, Newcomb C, Guevara JP, Cziraky MJ, Strom BL, Hennessy S. ADHD Medications and Risk of Serious Cardiovascular Events in Adults. Pharmacoepidemiol Drug Saf. 2011; 20:S122 (abstract 282).

[17] Centers for Disease Control and Prevention (CDC). Increasing prevalence of parent-reported attention-deficit/hyperactivity disorder among children --- United States, 2003 and 2007. MMWR Morb Mortal Wkly Rep. 2010;59:1439-43.

[18] Zito JM, Safer DJ, dosReis S, Magder LS, Gardner JF, Zarin DA. Psychotherapeutic medication patterns for youths with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med. 1999;153:1257-63.

[19] Fortuna RJ, Robbins BW, Caiola E, Joynt M, Halterman JS. Prescribing of controlled medications to adolescents and young adults in the United States. Pediatrics 2010;126:1108–1116.

[20] Brenner H, Arndt V, Gefeller O, Hakulinen T. An alternative approach to age adjustment of cancer survival rates. European Journal of Cancer. 2004; 40: 2317-2322.

[21] Liberthson RR. Sudden death from cardiac causes in children and young adults. N Engl J Med.

1996;334:1039-1044.

[22] Pike MC, Anderson J, Day N. Some insights into Miettinen's multivariate confounder score approach to case-control study analysis. Epidemiol Community Health. 1979;33:104-6.

[23] Garbe E, Suissa S. Hormone replacement therapy and acute coronary outcomes: methodological issues between randomized and observational studies. Hum Reprod. 2004;19:8-13.

[24] Cascade E, Kalali AH, Weisler RH, Lenderts S. Seasonality and the changing adult/child prescription ratios in ADHD therapy. Psychiatry (Edgmont). 2008;5:23-5.

[25] Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. Pharmacoepidemiol Drug Saf 2010;19:563-72.

[26] Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003;158:915-20.

[27]Berger JS, Lala A, Krantz MJ, Baker GS, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: A meta-analysis of randomized trials. Am Heart J. 2011;162:115-124.e2.

[28] James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C, Sharma AM, Shepherd GM, Rode RA, Renz CL; SCOUT Investigators. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med. 2010;363:905-17.

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