U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL SAFETY REVIEW AND EVALUATION

OBSERVATIONAL STUDIES

NDA/Serial Number:	N/A-Drug Class Review-Link TSI#114: SAFETY-000114 Attention Deficit Hyperactivity Disorder Drugs Safety Issue: cardiovascular disorders in children and youths
Drug Name:	Multiple treatments for attention deficit hyperactivity disorder (ADHD)
Applicant:	N/A
Document Review	Final Report for Observational Study: Attention Deficit Hyperactivity Disorder Medications and Risk of Serious Cardiovascular Disease in Children and Youth
Date(s):	April 29, 2011
Biometrics Division:	Division of Biometrics 7
Statistical Reviewer:	Bradley McEvoy, MS, DrPH
Concurring Reviewers:	LaRee Tracy, MA, PhD, Team Leader Mark Levenson, PhD, Deputy Division Director
Medical Division:	Division of Psychiatry Products, OND Office of Epidemiology and Surveillance (OSE)
Clinical Team:	Andrew Mosholder, MD (OSE), Kate Gelperin, MD (OSE), David Graham, MD (OSE), David Ritter, MD (DPP)
Project Manager:	Kristin Phucas (OSE)

Keywords: Observational study, propensity scores, ADHD medications, sudden cardiac death, stroke, myocardial infarction, outcome study, pediatrics

Table of Contents

List of Tables

List of Figures

1 Executive Summary

Concerns have been raised that the medication used to manage attention deficit hyperactivity disorder (ADHD) is associated with an increase in cardiovascular adverse events. In 2006 the Food and Drug Administration (FDA) and the Agency for Healthcare Research and Quality (AHRQ) co-funded separate studies in children and adults to investigate these drugs association with acute myocardial infarction (AMI), stroke and sudden cardiac death (SCD), which relied on data from multiple healthcare databases. On April 29, 2011 the child study final report titled, "Attention Deficit Hyperactivity Disorder Medications and Risk of Serious Cardiovascular Disease in Children and Youth" was submitted to FDA. This review addresses the child study.

The child study used a retrospective observational cohort design to compare risk in children age 2 to 24 who received an ADHD medication (current users and non-current users) to those who did not (non-users).

Of the 85 serious cardiovascular events that occurred during 2,579,104 patient-years of follow-up, 7 events occurred in current ADHD users (1.87 events per 100,000 patient years), 26 occurred in noncurrent ADHD users (4.28 events per 100,000 patient years) and 52 in non-users (3.25 events per 100,000 patient years). Among events in current users, all were reported by Medicaid sites (Tennessee and Washington) and occurred after a year in the study; cumulative ADHD medication exposure among these subjects ranged from 0.86 years to 6.82 years. Among the incident ADHD medication users there were 4 cardiovascular events in the current users (2.08 events per 100,000 patient years) and 20 in non-current users (5.31 events per 100,000 patient years).

Overall, the hazard ratio (HR) comparing current users versus non-users was 0.67 with a confidence interval (CI) that includes the null value (95% CI = 0.28, 1.64). In the incident user analysis that excluded prevalent ADHD users, the estimated hazard ratio comparing current users to non-users was 0.67 and the CI included 1 (95% CI=0.22, 1.99).

Event rates and estimated risks varied across healthcare sites. Estimates of risk from data from the public healthcare databases, Tennessee and Washington Medicaid, systematically differed from estimates derived from the private healthcare sites. This finding is potentially associated with differences between the Medicaid and non-Medicaid populations.

Beyond data quality limitations inherent in investigations of healthcare databases, the study design has the potential for generating biased results arising from the inclusion of prevalent ADHD users into the sample. The specific bias that prevalent users may introduce include under ascertainment of events that occur early in therapy (prior to study entry) and the inability to control for disease risk factors that might be altered by the drug therapy (Ray Am J of Epi, 2003; 159 (9)). The incident user sensitivity analysis is considered the most credible analysis performed since it is not vulnerable to prevalent user bias.

In addition, the broad patient inclusion criteria, which did not require a diagnosis of ADHD, resulted in a non-user comparison group that 1) may not yield clinically relevant comparisons since a sizable

number of non-users would likely not receive an ADHD medication, and 2) is characteristically different from the ADHD medication user groups. Furthermore, differences in health care utilization between users and non-users may have resulted in differential coding since it is more likely that a user was treated more recently (and perhaps more frequently) by a health care provider than a non-user. These differences can result in the non-users appearing healthier than the user group due to a lack of reported medical conditions. Finally, it is not apparent from the study report or protocol if site was included in the matching algorithm and therefore site-specific differences might exist among matched patients.

The final report lacks in sufficient detail required to fully evaluate the study, including a lack of statistical diagnostics, and an inadequate description of the study sample and events. Additional limitations include 1) major protocol deviations not mentioned in the final report, 2) incorrect interpretation of cohort characteristics of non-users at baseline, and 3) no unadjusted summaries of the non-user sample at baseline. Study data were unavailable to FDA reviewers; therefore, additional analyses could not be generated as well as study results could not be replicated.

In conclusion, study findings that the estimated cardiovascular risks were lower in current users compared to non-users of ADHD medication have to be interpreted within the confines of the study limitations and the sub-optimal data-streams. Given the deficiencies associated with the study design, analysis and an inadequate study report, the reviewer recommends 1) no comparative conclusions be drawn from analyses provided, and 2) the incident user incidence rate should be the only risk summaries considered, but with caution given the lack of detail in the final report. In addition, the low rate of cardiovascular events among patients that received an ADHD medication is a useful finding despite concerns regarding lack of valid comparisons with non-users.

2 Introduction

2.1 Overview

Concerns have been raised that the medications used to treat attention deficit hyperactivity disorder may be associated with an increase in cardiovascular (CV) adverse events. In 2006 FDA and AHRQ co-sponsored separate observational retrospective cohort studies in children and adults to investigate the association between exposure to ADHD medications and CV outcomes (specifically the occurrence of sudden cardiac death, acute myocardial infarction and stroke) using multiple healthcare databases.

The adult study was partitioned into two separate studies with different scheduled completion dates; one study investigated acute myocardial infarction (AMI) and sudden cardiac death (SCD) endpoints, and the other study investigated stroke events. The adult stroke study was completed on July 22, 2011; the child and adult AMI-SCD studies were completed on April 29, 2011.

The Office of Surveillance and Epidemiology (OSE) requested two statistical safety consultations from the Division of Biometrics 7. The first consult, received March 4, 2009, commented on the child study's statistical analysis plan described in the study protocol (version 4.3, date: 10/31/2008; review completed June 12, 2009). The adult study analysis plan closely resembled the plan for the child study and was not reviewed. The second consult, received September 15, 2010, requested continued participation on the study team, and to provide comments and review the draft and final study reports for both the adult and child studies.

This review provides a statistical evaluation of the April 29, 2011 final study report and supporting documents for the child study. This review does not incorporate revised results that removed four incorrectly classified stroke events; this error was communicated to FDA July 1, 2011, and the revised Tables were provided to FDA August 11, 2011. The statistical reviewer is conducting a separate review for the adult study.

2.2 Data Sources

On April 29, 2011 the principal investigator for the ADHD child study (Dr. William Cooper, Vanderbilt University) submitted to FDA the final study report entitled "Attention Deficit Hyperactivity Disorder Medications and Risk of Serious Cardiovascular Disease in Children and Youth". This review additionally references the draft study report (date: 11/30/2010), study protocol (version 4.5, 10/28/2009) and supplemental information requested by FDA based on draft study reports.

For completeness, Section 5.1 includes all study material provided to FDA by the principal investigator from the revised analysis that excluded the four misclassified strokes. Note that the revised Tables are only a subset of the Tables included in the April 29, 2011 final study reported.

Statistical Comment: Study data were not provided to FDA reviewers; therefore, the study results could not be replicated.

3 Statistical Evaluation

3.1 Data Analysis and Quality

Data were not submitted for review and therefore the quality of data can not be assessed.

3.2 Evaluation of Safety

3.2.1 Study Design

The study was an observational retrospective cohort study that used data from computerized health records originating from four unique sites: Tennessee State Medicaid, Washington State Medicaid, Kaiser Permanente California (Northern and Southern Regions), and Ingenix i3 (data from United Healthcare). The follow-up interval differed by site based on the earliest availability of the site's computerized data, as shown in Table 1. The Tennessee Medicaid site contributed the longest period of times.

Table 1. Study period by site

Site	Study Period
Tennessee Medicaid	1986-2005
Washington Medicaid	2000-2005
Kaiser Permanente	1999-2005
Ingenix i3	1998-2005

Cohort of eligible person-time was assembled from the enrollees of each health plan who were age 2 to 24, had availability of data needed for the study (*from draft report:* including requirements for

continuous enrollment in the 365 days prior to the beginning of follow-up to allow for complete ascertainment of study variables), and an absence of a very serious illness. Very serious illness included sickle cell disease, cystic fibrosis, cerebral palsy, cancer, HIV infection, organ transplant, liver failure, renal dialysis, respiratory failure, or other potentially lethal diseases of childhood. Additionally, cohort members could not have a hospital discharge in the preceding 365 days with a primary diagnosis of acute myocardial infarction or stroke.

Cohort eligibility ended the earliest of the following dates: 1) the last day of the study, 2) when the cohort member reached the upper age limit for the study, 3) the last day of membership of pharmacy benefits in a plan, 4) the day prior to development of an exclusion illness, or 5) the day of death.

The sample included all subjects with eligible patient-time of ADHD medication use. Patient follow-up began for a subject at their earliest cohort eligible day of ADHD medication use, defined as t_0 and referred to as baseline. Subjects that received an ADHD medication prior to becoming cohort eligible were not excluded from the sample and are referred to as prevalent users. The formation of the cohort was done in chronological sequence starting at the earliest calendar day of eligible ADHD medication use. A random sample of person-time from two cohort members with no evidence of ADHD medication use on that date were matched at t_0 using birth year and gender. It is not evident from the final report or protocol if matching users to non-users was done within site. Subjects matched to an ADHD user are referred to as non-users. By allowing the pool of possible non-users that could be matched to a user to include subjects that will eventually use an ADHD medication, a non-user could switch user status and become an ADHD medication user. In the event of a switch from non-use to use status, that patient was then matched to two subjects who had no evidence of ADHD medication use on the day of the switch.

It is unapparent from the report or protocol if matching was done within site. The implication of not matching within site is potentially problematic since there are known differences across sites including distribution of health disparities and treatment practices.

The design permitted a subject that lost cohort eligibility (e.g., had a very serious illness) to contribute additional patient-time after regaining cohort eligibility. For a ADHD user that re-entered the cohort he would be matched to two non-users.

Reviewer's Comments: The design choices to include prevalent users and include varying site eligibility periods were made to "maximize study power" as per the investigators. These choices, unfortunately, resulted in the sample (thereby, comparisons) susceptible to bias.

The biases associated with including a patient that used an ADHD medication prior to becoming cohort eligible (i.e., a prevalent user) are well established. Inclusion of prevalent users is not recommended as it can result in an under ascertainment of events that occur early in therapy and fails to control for disease risk factors that might be altered by the drug therapy (R. Way, Am. J. Epidemiology 2003; 915-920).

The potential for prevalent-user bias in the study 1) may be differential across study sites, and 2) is large since almost half of the ADHD users were prevalent users at baseline.

Systematic differences between ADHD users and non-users (some of which were not measured) could confound any observed association between ADHD medication exposure and the outcome.

The statistical reviewer disagrees with the investigators' assessment that non-users of ADHD medication represent the best choice for a comparison group for the primary analysis (stated in the final report, page 12); the chosen reference group is largely driven by the limitations of the data-stream. In other words, the investigators are suggesting that it would be difficult to identify a control group of adequate size that does not use ADHD medication but has the disease(s) for which ADHD medication is typically prescribed. The problem with this design is that the probability of receiving treatment is largely driven by the patient's disease characteristics. In addition, it is more likely that a user was more recently treated (and possibly more frequently) by a health care provider than a non-user. This could contribute to differential health care utilization between users and non-users and differential coding of patient characteristics and outcomes resulting in the non-users appearing 'healthier' than the user group due to a lack of reported medical conditions (that may be considered confounders in the analysis).

The statistical reviewer disagrees with the investigators' claim in the final report (page 12) that "All persons who were non-users at baseline had the possibility of becoming users during follow-up". This claim is unsupported by the pattern of patient characteristics in the non-user group, which suggests that most non-users had a little or no chance of receiving an ADHD medication. Moreover, this statement implies the study design fulfills a propensity score modeling assumption that all patients have a true non-zero probability of receiving an ADHD medication. The statistical reviewer's concerns with the study design, as it relates to the modeling assumptions, were communicated to the investigators during the study.

3.2.2 Exposure Status

Every person day during the study follow-up was classified according to probable use of an ADHD medication. Table 2 shows four groups of ADHD medication use status based on current use and time since last use. Subjects that discontinued ADHD medication are considered non-current users (i.e., indeterminate, former or remote users). For each prescription filled, the number of days of use was estimated by defining the start of the prescription as the fill date and adding the days of use of the prescription to the fill date. Overlapping dates of use for the same or different ADHD medication allowed up to 7 days of cumulative stockpiling, under the assumption that the overlapping did not represent current use.

Table 2. Classification of ADHD medication use status

ADHD use status	Period Description
Current use	Time between the prescription start date and the end of the days supply
Indeterminate use	Day after current use and lasting for 89 days
Former use	Between 90 and 364 days after last day of current use
Remote	365 days after last day of current use through the end of study follow-up

†Current use include incident and prevalent users

3.2.3 Study Endpoints

The reported primary study endpoint is serious cardiovascular disease, which is a composite endpoint including sudden cardiac death, myocardial infarction and stroke. Potential events were adjudicated by at least two adjudicators according to a predefined clinical definition. Case status for potential events, with medical records, that could not be adjudicated was determined by a computer case definition.

Reviewer's Comment: The protocol-specified primary endpoint was sudden cardiac death. The primary endpoint presented in the final study report (composite endpoint of SCD, AMI or stroke) was originally planned as a secondary endpoint. Although FDA reviewers recommended that this major change be discussed in the final study report, no such discussion or justification is provided. This change in the primary endpoint was likely made due to the few observed events of SCD; however, failure to acknowledge this major protocol deviation in the final study report is a major limitation. In addition, since the change was due to the low event rate in the originally planned endpoint, this raises concern regarding the overall legitimacy of the final comparisons.

There was concern regarding how cases of AMI and SCD were identify and confirmed in this study. Refer to the clinical review by Dr. Andrew Mosholder for details on these issues.

3.2.4 Statistical Methodology

Primary Analysis

Cox proportional hazard (PH) regression was used to compare the adjusted incidence of the study endpoint across the different ADHD medication use statuses. Non-users were selected in the model to serve as the primary reference group. To account for the matched study design and for the possibility that the same patient can become cohort eligible more than once, the analysis utilized sandwich variance estimators. The final study report states the regression model included, as covariates, propensity score deciles, site, age, calendar year, and time-dependent exposure status and covariates. Time-dependent covariates included medical hospitalization, general medical care access, major psychiatric illness, substance abuse, antipsychotic use, serious chronic illness, and other cardiovascular disease. Details of the propensity score analysis are described below.

The proportionality assumption was checked by testing a time-by-exposure interaction term. According to the study report there was no detectable departure from the proportionality assumption for any model (results not provided).

Reviewer's Comments on the primary analysis: The protocol-specified primary statistical analysis included the use of Poisson regression. This major protocol deviation was not discussed in the final study report.

The final report and Table footnotes incorrectly state that calendar year was included as covariate. The investigators were informed of this error; however, this error was not corrected.

PH analyses that included prevalent users are inherently flawed. The problem is the timing of events and time-dependent covariates are in relation to time-in-study, not time-on-drug. In other words, the characterization of risk of ADHD medication for a prevalent user is not in relation to treatment initiation (which is the case for a randomized clinical trial and for incident users). This difference in

timing, which is an unknown quantity, makes the regression estimates potentially biased. In addition, the initiation of follow-up for non-users is arbitrary.

The ability of the sandwich variance estimator to account for the design features is questionable given the sparseness of the primary endpoint, the large number of model parameters, and an incorrectly specified working correlation matrix. Due to small number of events, the asymptotic properties of the sandwich variance estimator can not be assumed. An incorrectly specified working correlation matrix will likely result in standard error estimates that are too small. It appears an independent working correlation matrix was assumed, which does not account for the design feature that a subject could have multiple cohort eligibility periods.

Inclusion of PS deciles in the regression model is not ideal as the treatment effect estimation is not conditional on the PS value. In contrast, in a stratified analysis the treatment comparison is derived among patients with a similar likelihood of receiving the treatment.

When interpreting study results one should consider whether the time-varying covariates satisfy the general recommendation that they should not be affected by exposure (R. Way, Am. J. Epidemiology 2003; 915-920).

Propensity Score Analysis

Propensity scores (PS) were estimated and used in an attempt to adjust for measured confounders. The PS was defined as the probability that a patient was a current ADHD user on the first day of study follow-up given the observed baseline covariates. By definition, a prevalent user's baseline covariates include post-treatment measurements. PS were not recalculated when a subject changed ADHD user status. Therefore, since PS were only calculated for an individual upon entry into the study, for a non-user that became a user, that subject's PS are based on covariates values when they were selected as a match and not according to when they received treatment. The report does not state if PS were recalculated for a subject after re-entering the cohort after regaining cohort eligibility.

PS were calculated separately at each site and were subsequently pooled across sites. Pooling PS across sites assumes a patient in a given PS decile in one site is "equivalent" to another patient in the same PS decile from a different site. The report did not discuss modeling strategies for building the PS model.

A method, referred to as the Brenner method (Brenner, et al., European J. of Cancer, 2004, 2317-22), was used to evaluate site-specific covariate balance. The Brenner method attempts to show what the non-users sample at baseline would have looked like if the non-users had the same allocation of subjects by PS decile as the current-user group. Formally, the Brenner method weights the non-user decile-specific estimate by the proportion of the overall sample of current users in that decile. If the decile-specific estimates are the same between groups for each decile, then the Brenner adjusted estimate for the non-user will equal the unadjusted estimate for the current user group, and thereby, resulting in covariate balance. See comment 3 below regarding the validity of this method to assess balance.

Reviewer Comments:
1) The protocol specified that confounder risk scores (CRS) be used rather than propensity scores (study protocol, page 65). The protocol further states if CRS are not implemented, simpler models will be fit that adjust for age, sex, race and prior event history (page 64). Although the PS methodology is a more established methodology than CRS and its use is reasonable in this study design, these changes in the analyses were not discussed in the final report as requested by FDA.

2) Two PS model assumptions were violated. The first assumption, as a consequence of including prevalent users instead of incident, is that the PS model incorrectly adjusts for post-treatment measurements. The potential consequences of this are a misclassification of subjects into PS deciles, and biased risk estimates resulting from controlling for variables that may fall along the causal pathway of the primary endpoint. The second assumption violated, which was a result of the broad inclusion criteria, is that each patient must have a true non-zero probability of receiving an ADHD medication. (A distinction is made between the true and estimated propensity score). The proportion of patients in the non-user comparison group with an ADHD diagnosis (a factor likely to predict receiving an ADHD medication) was only 1.3%. Since this proportion is extremely small, the reference group likely includes a sizable number of patients that would never have any chance of receiving the drug. The first of the violated assumptions can easily be addressed by limiting the study to incident users. The second violation, however, would be difficult to resolve with the current design. Conceivably, a more ideal study cohort would include only patients with a diagnosis of ADHD. However, it might be difficult to identify a non-user treatment group in this cohort given that most, if not all, patients will have current or past exposure to an ADHD medication.

3) Covariate balance at baseline can not be evaluated since it requires evaluating decile-specific summaries, which were not provided. From the Brenner adjusted estimates alone it is not possible to conclude the decile-specific summaries are similar between groups, which is necessary since the PS theory assumes ADHD medication use and baseline covariates are independent within PS deciles. This is a crucial omission in the final study report given the need to balance covariates in an observation study design. This issue is further discussed in Section 5.4 including an example highlighting the deficiency of the Brenner method. Note, also that use of this method was not planned in the original protocol.

4) The PS model did not include a variable for diagnosis of ADHD. This is a major omission given that the unadjusted proportion of ADHD diagnosis was imbalanced favoring current users (57.4%) compared to the non-users (1.3%).

Summarizing Baseline Demographics

Comparison of current- and non-user baseline characteristics was based on the Brenner adjusted summaries for non-users and the unadjusted summary for current users. Unadjusted summaries for non-users at baseline were not provided in the final report.

Reviewer Comments: Use of the Brenner method to summarize the sample is seriously flawed since the Brenner weights were not incorporated into the main statistical analyses. As a result, the pseudo-population described in the final reports differs from the population in which the risk estimates are projected based on the Brenner methods. Incorporating PS deciles into the model does not correspond

with this approach, as a stratified or matched analysis would. Use of weights was not specified in the study protocol.

The characteristics of the non-user sample at baseline can not be evaluated in the final report (in the body or Appendix) since only the Brenner adjusted estimates were provided. Without the unadjusted summaries, the results are difficult to interpret. To address this shortcoming of the final report, this review provides unadjusted summaries obtained from earlier draft reports and communications.

Sensitivity Analyses

Table 3 lists several analyses that were performed to evaluate possible limitations of the study design.

Table 3. List of Sensitivity Analyses and study design limitation addressed

Sensitivity Analysis	Limitation addressed	Exposure	Reference
Primary Analysis*		Current	Non-user
Comparison Group			
Former user as reference	Unmeasured confounding	Current	Former
Exposure Group Definition			
Restricted to incident users	Covariates measure at drug initiation	New	Non-user
Recent users as exposure group	Prodrome could change exposure	Recent	Non-user
Carry over users status at entry	Effects of prior exposure status on risk	Current	Non-user
Handling of Covariates			
Individual covariates, no PS	PS performance	Current	Non-user
Psychiatry utilization in model, not in PS	PS performance	Current	Non-user
Stratified by prior psychiatric care utilization	PS performance	Current	Non-user
Exclude psychiatric utilization care	psychiatric utilization variable	Current	Non-user
Fix time-dependent variables at baseline	Covariates on causal pathway	Current	Non-user
Case definitions			
Include cases excluded for severe underlying cardiac disease	Effects of underlying cardiac disease	Current	Non-user
Potential differences in sites			
Restrict analyses to 2000-2005	Differences based on available data	Current	Non-user

† Recreated from Table 5 from final report; *Primary analysis compared outcome between current and non-users

Reviewer Comments: The following are several issues/considerations for the analyses summarized in Table 3.

1) *The reviewer considers the incident user analysis the most valid and credible analysis in the report since it is not vulnerable to the biases associated with including prevalent users. The additional uncertainty (due to the wider confidence interval due to smaller sample size) in the risk estimate from the incident user analysis, which is not inherently susceptible to bias, is statistically more appropriate. The increased precision from the full sample analysis is not ideal as the narrower confidence interval will be centered on a potentially biased risk estimate.*

2) *Results from three secondary protocol-specified comparisons were not presented in the final report. These planned analyses include 1) comparison in children less than 18 years of age*[1]*, 2)*

[1] Three (3) out of the 7 events among current users occurred in children 18 or older. Summary information for the other exposure groups was not provided. Source: supplemental material received 2/24/2011.

subgroups analysis by psychiatric comorbidities, and 3) subgroup analyses defined by cardiovascular comorbidities.

3) *Alternative analyses were performed after viewing the final study results and should, therefore, only be considered exploratory. The alternative analyses include those related to Handling of Covariates and Addressing Case Definitions described in Table 3 above.*

4) *The sensitivity analyses are inadequate to evaluate the overall net contribution of design choices since they do not account for multiple potential biases concurrently. Instead, these analyses isolate a marginal effect of one source bias while ignoring other sources of bias present in the data. For example, an analysis that restricted data from 2000 to 2005 in the comparison of current vs. non-users is still vulnerable to prevalent user bias.*

5) *The report did not elaborate how changing the reference group would address potential biases since no subjects were excluded from the analysis. Moreover, this analysis does not provide information that could not have been obtained from the primary analysis. That is, the comparison of current-users to non-current users could have been directly obtained from the primary analysis by performing a contrast of the model coefficients.*

6) *The analysis that adjusted for covariates instead of PS may have resulted in biased risk estimates since there were nearly as many parameters included in the model (70) as there were endpoints observed (85).*

7) *The rational for investigating psychiatric utilization was not mentioned in the final report, but is described here. This variable was identified for further investigation by FDA after reviewing preliminary study findings since 1) it was highly predictive of treatment assignment in the PS models, and 2) cardiovascular events among current users occurred in patients with large estimated propensity scores. In the site-specific PS models the estimated odds ratio for treatment assignment ranged from 19.1 to 59.7.*

3.2.5 Results

Disposition and Follow-up

In total, data from 1,200,438 children were assessed in this retrospective study, of which 400,157 were classified as current users, 6,967 as non-current users and 793,317 as non-users at baseline or t_0. Table 4 shows the number of patients at baseline, by site, and ADHD medication use status. Ingenix was the largest site, followed by Tennessee Medicaid, Kaiser CA and Washington Medicaid.

Table 4. Number of patients at baseline by site and ADHD medication use status

Site	Total N	Non-user n	Non-current n	Current n
Overall	1,200,438	793,314	6,967	400,157
Ingenix i3	692,187	457,809	3,690	230,688
Tennessee Medicaid	200,198	133,314	208	66,676
Kaiser CA	191,772	127,071	660	64,041
Washington Medicaid	116,281	75,120	2,409	38,752

Reviewer Comment: The study does not appear to have 1,200,438 unique children since the same subject would have been recounted if he/she left and re-entered the cohort. The final report states 1.2% of the sample left and reentered the cohort, resulting in approximately 15,000 fewer unique patients in the study as reported. This figure can not be verified given the limited information provided in the final study report.

Among current users, almost half (48.5%) were prevalent users at baseline. Table 5 shows the Tennessee site (which has the earliest eligibility time) with 11.3% of the sample as prevalent users. The other sites (eligibility began between 1998 and 2000) had between 46.5% and 60.4% of the sample as prevalent users. Reason for this variation is unknown and was not addressed in the final report. One possible explanation is varying site eligibility periods. These numbers were provided in supplemental material received 1/15/2011 and do not appear in the final report, which is a major omission given the potential for bias relating to inclusion of prevalent users.

Table 5. Number of current users that used an ADHD medication in the 365 prior to t_0

Site (# Current users at baseline)	Incident users n (%)	Prevalent users n (%)
Overall (N=400,157)	205,984 (51.2)	194,173 (48.5)
Tennessee Medicaid (N=66,676)	59,108 (88.7)	7,568 (11.3)
Kaiser CA (N=64,041)	34,877 (54.5)	29,164 (45.5)
Ingenix i3 (N=230,688)	91,329 (39.6)	139,359 (60.4)
Washington Medicaid (N=38,752)	20,670 (53.3)	18,082 (46.7)

† Page 55-57 from response to FDA information request received 1/15/2011

‡ Number of prevalent and incident users estimated from proportion of currents users that used ADHD medication in 365 days prior to t_0

Reviewer Comment: Although requested by FDA, the final report does not describe dynamics of the study cohort, including how many patients switched from non-use to current ADHD medication use status, change in use status after a patient re-entered the cohort, and how many patients contributed to patient time in the non-current use group. In the absence of this information and the complexity of the cohort entry design (i.e., subjects switching exposure status, and leaving and reentering the cohort) results are difficult to interpret.

Demographics

Table 6 shows overall cohort characteristics for current and non-users at baseline. Characteristics for non-users include both the unadjusted and Brenner adjusted estimate. *Note the unadjusted non-user summaries were not provided in the final study report.* See Section 5.1 for site specific summary of

patient characteristics. *Note that the cohort characteristics for the Washington Medicaid site presented in the report are a duplicate of the cohort characteristics presented for the Ingenix i3 site. Summaries in this review are correct.*

By design, non-users and current-users at baseline had the same age (mean of 11 years) and gender (71% male). Other patient characteristics tended to differ considerably between groups. A larger percentage of current-users vs. non-users at baseline had asthma (22.1% vs. 16.1%), minor congenital heart defects (6.9% vs. 3.6%), a diagnosis of ADHD (57.4% v. 1.3%), and mental retardation (4% vs. 0.6%). Current users were more likely than non-users to have a prescription filled at baseline for antidepressants (15% vs. 1.8%) or antipsychotics (5.2% vs. 0.4%), have used psychiatric care in the 365 days prior to baseline (63.1% vs. 5.4%) and have received any outpatient visit (92.9% vs. 75.1%).

The non-user Brenner adjusted estimates were reasonably similar with the unadjusted estimates for the current users, but were markedly different from their corresponding unadjusted estimate.

Reviewer's Comment: The final report incorrectly interpreted the Brenner adjusted estimates as describing non-user characteristics at baseline. For instance, the final report states that non-users were more likely to have a filled prescription for antidepressants (17.2% vs. 15%), which contradicts the interpretation using the unadjusted summaries (1.8% vs. 15%). This interpretation of non-user characteristics in the report, along with the absence of unadjusted non-user summaries in the report and no formal description of the Brenner method, gives a false impression that the sample of non-users and current-users are similar with respect to measured covariates when they are significantly different. Had the Brenner weights been incorporated into the statistical analysis it would have been appropriate to describe the non-user sample in this manner; however, since this was not done, the authors' interpretation of cohort characteristics is seriously flawed.

Table 6. Adjusted and unadjusted cohort characteristics at baseline pooled across sites

	Non-user		Current-user
	Unadjusted %	Brenner %	Unadjusted %
Child characteristics			
Age in years, mean	11.1	11.4	11.1
Male	70.9	70.7	71.1
Non-white	79.1	33.2	36.8
Reside in metropolitan area	33.2	76.7	77.1
Medical conditions			
Asthma	16.1	26.7	22.1
Seizures	0.6	2.5	2.1
Life threatening conditions	0.8	1.7	1.3
Obesity	0.9	1.3	1.2
Major congenital heart defect	0.5	0.9	0.8
Minor congenital heart defect	3.6	7.3	6.9
Diabetes	0.4	0.6	0.5
Diabetes, poor control	0.1	0.2	0.2
Psychiatric conditions			
ADHD diagnosis	1.3	15.8	57.4
Major depression	1.6	11.8	10.4
Bipolar disorder	0.2	1.9	2.1
Psychosis	0.1	0.6	0.5
Autism	0.2	1.3	1.4
Mental retardation	0.6	2.9	4
Severe mental retardation	0.01	0	0
Prior suicide attempt	0.07	0.3	0.3
Psychotropic medication use			
Antidepressants	1.8	17.2	15
Mood stabilizers	0.5	4	4.2
Antipsychotics	0.4	4.4	5.2
Benzodiazepines	0.09	0.6	0.5
Alcohol and drug use			
Alcohol use	0.2	0.7	0.6
Cocaine use	0.02	0.1	0.1
Opiate use	0.02	0.1	0.1
Smoking	0.6	1.2	0.9
Other drug abuse	0.3	1.2	1.1
Use of health services			
Psychiatric hospitalization	0.3	2.2	1.9
Medical hospitalization	2.5	4.6	4.1
Medical emergency department visit	12.9	16.8	15.8
Any psychiatric care	5.4	55	63.1
Any cardiovascular care	4	6.7	6
Any outpatient visit	75.1	93.3	92.9
Any prescription	22	37	31.7

Propensity Scores Analysis

The distribution of site-specific PS for current and non-users at baseline are displayed in Section 5.3. For all sites the PS distribution for non-users tended to be near zero and bimodal with mass at the extremes (0 and 1) for current-users. The variable psychiatric utilization (`xanypsych`) was highly predictive of receiving an ADHD medication in each site. In the final report it is concluded that propensity scores were able to balance users and non-users at baseline.

Reviewer Comments: The claim that propensity scores achieved balance can not be confirmed with information provided either in the report or supplemental material. Therefore, we cannot conclude/assume the statistical benefits afforded by PS (i.e., control for confounding) are realized.

The disparate PS distributions support our concern that current users and non-users study populations are characteristically different. The plots additionally support the concern that non-users have little to no probability of having received an ADHD medication given the observed covariates (as suggested by the PS scores skewed toward zero).

In general, given the biases associated with the inclusion of prevalent users into the current user group, the appropriateness of investigating covariate balance for the full sample is suspect. The adequacy of the incident user (sensitivity) analysis, which is more likely to eliminate some of the concerning biases associated with prevalent users, can not be evaluated. This final study report lacks in results from pertinent diagnostics necessary and requested (by FDA) to assess this analysis.

Overall Results

Table 7 shows events counts for the composite endpoint and its components by user status. From the 2,579,104 patient years of follow-up there were 85 total serious cardiovascular events (3.30 events per 100,000 patient years); among non-users there were 52 events (3.25 events per 100,000 patient years), 7 events among current users (1.87 events per 100,000 patient years) and 26 events occurred after subjects stopped receiving an ADHD medication (4.28 events per 100,000 patient years). Of the 7 serious cardiovascular events occurred in current users, 3 were sudden cardiac deaths and 4 were stroke; by type of ADHD medication, 4 events were in subjects prescribed methylphenidate, 1 with amphetamines, 1 with atomoxetine and 1 with pemoline.

Table 7. Event counts and rates by site, event type and ADHD user status

Event by Site	Overall n (rate/100,000 py)	Non-user n (rate/100,000 py)	Non-current n (rate/100,000 py)	Current n (rate/100,000 py)
Full Sample (py)	2,579,104	1,597,962	607,475	373,667
Serious Cardio. Events	85 (3.3)	52 (3.5)	26 (4.28)	7 (1.87)
Sudden Cardiac Death	33 (1.3)	17 (1.1)	13 (2.1)	3 (0.8)
Myocardial Infarction	9 (0.3)	6 (0.4)	3 (0.5)	0 (0.0)
Stroke	43 (1.7)	29 (1.8)	10 (1.6)	4 (1.1)
TN Medicaid (py)	776,048	470,853	227,655	77,541
Serious Cardio. Events	46 (5.9)	29 (6.2)	14 (6.2)	3 (3.9)
Sudden Cardiac Death	21 (2.7)	14 (3.0)	5 (2.2)	2 (2.6)
Myocardial Infarction	5 (0.6)	3 (0.6)	2 (0.9)	0 (0.0)
Stroke	20 (2.6)	12 (2.5)	7 (3.1)	1 (1.3)
Kaiser CA (py)	508,082	329,872	100,436	77,773
Serious Cardio. Events	14 (2.8)	10 (3.0)	4 (4.0)	0 (0.0)
Sudden Cardiac Death	8 (1.6)	6 (1.8)	2 (2.0)	0 (0.0)
Myocardial Infarction	2 (0.4)	1 (0.3)	1 (1.0)	0 (0.0)
Stroke	4 (0.8)	3 (0.9)	1 (1.0)	0 (0.0)
Ingenix i3 (py)	1,054,587	651,489	226,833	176,264
Serious Cardio. Events	16 (1.5)	11 (1.7)	5 (2.2)	0 (0.0)
Sudden Cardiac Death	10 (0.9)	7 (1.1)	3 (1.3)	0 (0.0)
Myocardial Infarction	2 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)
Stroke	4 (0.4)	2 (0.3)	2 (0.9)	0 (0.0)
WA Medicaid (py)	240,387	145,748	52,550	42,088
Serious Cardio. Events	9 (3.7)	2 (1.4)	3 (5.7)	4 (9.5)
Sudden Cardiac Death	4 (1.7)	2 (1.4)	0 (0.0)	2 (4.8)
Myocardial Infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke	3 (2.1)	0 (0.0)	3 (5.7)	2 (4.8)

py=patient-years

Reviewer Comment: Despite concerns of the potential for bias, the statistical reviewer believes the most important finding from this study is the small number of events that occurred among current users and non-current users.

Figure 1 and Figure 2 (produced by the reviewer given summary-level data provided in the supplemental material requested by FDA, which was not included in the final study report) show the ADHD medication use status history for current and non-current users who experienced an event, respectively. Among current users all the events occurred after the first year in the study; cumulative ADHD medication exposure among these subjects ranged from 0.86 years to 6.82 years. The cumulative ADHD exposure among the non-current subjects that had an event ranged from 0.04 years to 2.46 years; 7 of these subjects had a cumulative ADHD exposure for more than a year. Based on non-current use status, there were 5 events among indeterminate users (last day of current use + 89 days), 5 in former users (between 90 and 364 days after last day of current use) and 16 in remote users (365 days after last day of current use).

Figure 1. ADHD medication use status among the 7 current users that had an event

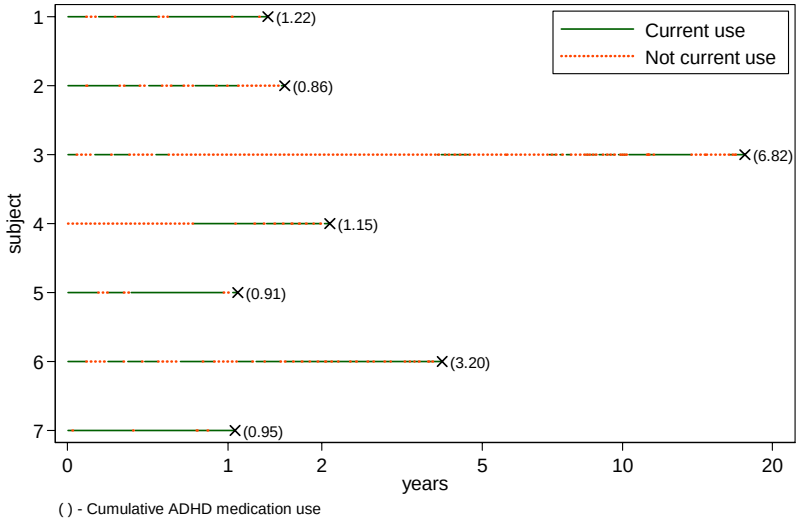


Figure 2. ADHD medication use status among the 26 non-current users that had an event

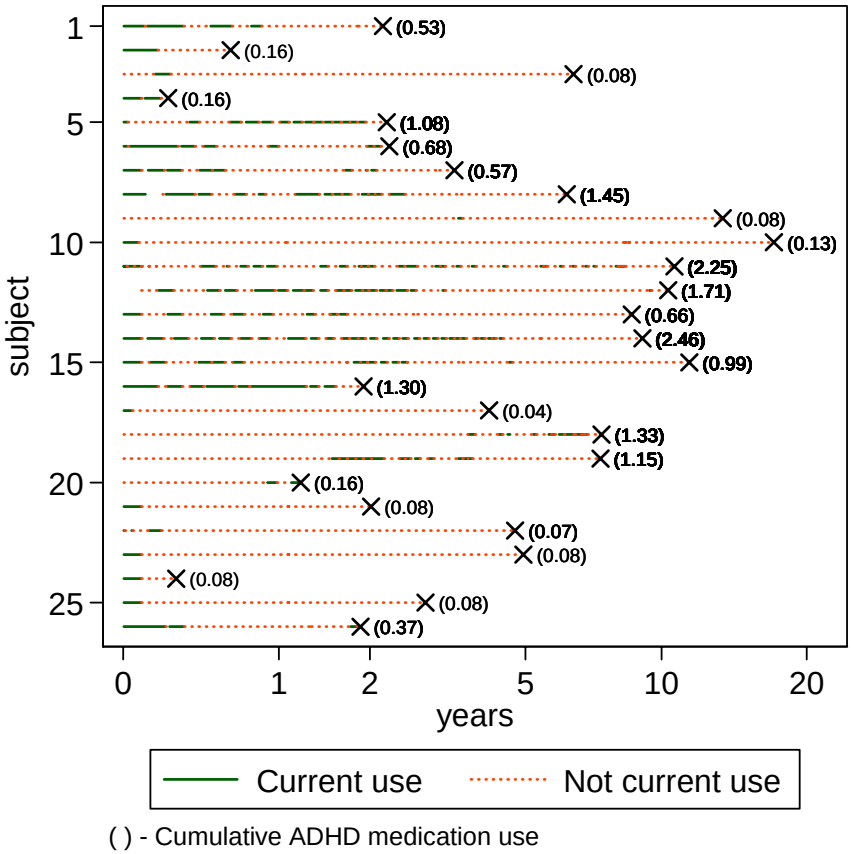


Table 8 shows the overall results for the full sample and site specific analyses. In the full sample subjects that were current users compared to non-users had a hazard ratio (HR) of 0.67 and a confidence interval (CI) include the null value 1 (95% CI = 0.28, 1.64). The estimated HR comparing non-current users to non-users was approximately one. By propensity score decile (pooled across sites), shown in Section 5.4, events among current users only occurred in patients in the 7th, 8th and 10th decile, while 40 of the 52 events in the non-users occurred in deciles 1 to 6. The absence of events among current users in the low PS deciles may suggest heterogeneous risks.

Table 8. Overall and site-specific time-to-event analysis

User group	Full Sample HR (95% CI)	TN Medicaid HR (95% CI)	Kaiser CA HR (95% CI)	Ingenix i3 HR (95% CI)	WA Medicaid HR (95% CI)
Current User	0.67 (0.28, 1.64)	1.15 (0.32, 4.16)	NE	NE	2.18 (0.35, 13.74)
Non-current	0.98 (0.55, 1.77)	1.12 (0.52, 2.41)	0.61 (0.13, 2.95)	0.95 (0.30, 3.04)	0.89 (0.17, 4.83)
Non-user	-	-	-	-	-

NE-Not estimable since no events, HR=Cox Proportional hazard ratio

Reviewer Comment: In the primary analysis the following three time-varying covariates yielded statistically significant estimated hazard ratios: psychiatric illness (HR=2.62; 95% CI=1.47, 4.77), serious cardiovascular disease (HR=5.51; 95% CI=2.49, 12.18) and serious chronic illness (HR=7.19; 95% CI=3.50, 14.78). The report does not note this relationship nor investigate the effect of ADHD medication when some or all of the time-varying covariates are removed from the model.

By Site Analyses

Most events were identified in the Tennessee site (46, 5.93 events per 100,000 patient years). There more events and a larger event rate the two Medicaid sites (TN and WA) compared to private insurance sites (Kaiser and Ingenix i3). All events among current users occurred in the Medicaid sites (four in Washington Medicaid and three in Tennessee Medicaid). Among patients that ever used an ADHD medication (non-current and current users) there were 6.00 events per 100,000 patient years in the Medicaid sites compared to 1.55 events per 100,000 patient years in the private sites. Among non-users the event rate was significantly greater in the Medicaid sites (31, 5.03 events per 100,000 patient-year) compared to the private sites (21, 2.14 events per 100,000 patient-years; rate ratio = 2.35, 95% CI =1.31, 4.30).

In the site specific analyses, only the two Medicaid sites contributed an estimate comparing current users to non-users. In both Medicaid sites the estimated hazard ratio for current users compared to non-users was greater than one with a confidence interval including unity. See Section 5.4 for events (and rates) by decile and site. In both Medicaid sites there was little overlap in the PS deciles where the events occurred between non-users and current users. Comments for the overall analysis regarding the heterogeneity and extrapolation of risk are applicable here.

Reviewer Comment: Despite the limited number of events, there were important site-specific features that were not discussed or investigated in the final report. For example, details are lacking regarding the finding that all current use events were from the Medicaid sites and fell into the higher PS deciles.

Incident User Sensitivity Analysis

There were 4 cardiovascular events among incident users from 192,040 patient years of follow-up (2.08 events per 100,000 patient years) and for non-current users there were 20 events from 376,456 patient years (5.31 events per 100,000 patient years). The type of events (i.e., stroke, sudden cardiac

death or myocardial infarction) and other details of the incident user events were not provided in the final report. The event rate was larger among the incident user group (4.22 per 100,000 patient years) that ever used an ADHD medication (current and non-current) compared to prevalent users that ever used an ADHD medication (2.18 per 100,000 patient years). Note the prevalent user event rate should be interpreted cautiously since not all exposure time was captured.

The estimated hazard ratio for serious cardiovascular disease among current user compared to non-users was 0.67 with a 95% confidence interval including one (0.22, 1.99). The magnitude of the risk estimate in this sample is similar to the risk estimate derived from the primary analysis. The estimated risk was slightly above one for non-current users compared to non-users (HR=1.09, 95% CI = 0.59, 2.04).

Reviewer comment: Although it is not explicitly stated in the report, PS were recalculated for the incident user analysis.

As previously stated, the reviewer considers the incident user analysis the most "valid/credible" analysis presented in the study report. However, this analysis has limitations including 1) imbalance of matching variables (i.e., age, gender and calendar year) resulting from the non-users that were matched to the prevalent users at baseline remained in the sample, and 2) study sites with differing eligibility periods. Furthermore, the results of this analysis can not be fully interpreted since pertinent information about the sample, the PS analysis, and description of events were not included in the final report.

Additional Sensitivity Analyses

Table 9 displays results from various sensitivity analyses summarized in the final report intended to evaluate the impact of various design/analysis choices. Across all sensitivity analyses results, the relationship observed for the current users compared to non-users were similar to the risk estimate derived from the primary and incident user sample and analysis. All of the risk estimates had CIs that included the null value.

Reviewer Comments: The ability of sensitivity analyses to evaluate the impact of various design/analysis choices is severely limited because they are vulnerable to prevalent-user bias and the overall low event rate. The similarity of the sensitivity analyses results with the results from the full sample does not provide the confirmation that the overall results are unbiased but rather that the overall results seem consistent.

Table 9. Sensitivity analyses

Analysis	Patient years	Events (rate/100,000 py)	HR (95% CI)
Former user as reference			
Former user	388693	21 (5.40)	-
Non-user	1597962	52 (3.25)	0.91 (0.54, 1.56)
Indeterminate user	218782	5 (2.29)	0.73 (0.27, 1.95)
Current user	373667	7 (1.87)	0.61 (0.24, 1.55)
Recent users as exposure group			
Non-user	1,597,962	52 (3.3)	-
Former user	388693	21 (5.4)	1.04 (0.54, 2.00)
Recent-user (current/indeterminate)	592449	12 (2.0)	0.70 (0.35, 1.42)
Carry over users status at entry			
Non-user	1,597,962	52 (3.3)	-
Non-current user	608037	26 (4.3)	0.98 (0.55, 1.76)
Current user	373242	7 (1.9)	0.67 (0.28, 1.64)
Individual covariate adjustment (no PS)			
Non-user	1,597,962	52 (3.3)	-
Non-current user	607475	26 (4.28)	Not Reported
Current user	373667	7 (1.87)	0.68 (0.29, 1.62)
Psychiatry utilization in model, not in PS			
Non-user	1,597,962	52 (3.3)	-
Non-current user	607475	26 (4.28)	Not Reported
Current user	373667	7 (1.87)	0.64 (0.27, 1.50)
Stratified by prior psychiatric care utilization			
Non-user	1,597,962	52 (3.3)	-
Non-current user	607475	26 (4.28)	Not Reported
Current user	373667	7 (1.87)	0.60 (0.25, 1.45)
Exclude psychiatric utilization care			
Non-user	1,597,962	52 (3.3)	-
Non-current user	607475	26 (4.28)	Not Reported
Current user	373667	7 (1.87)	0.59 (0.25, 1.37)
Time-dependent fixed variables at baseline			
Non-user	1,597,962	52 (3.3)	-
Non-current user	607475	26 (4.3)	0.99 (0.54, 1.81)
Current user	373667	7 (1.9)	0.81 (0.33, 1.99)
Include excluded cases for severe underlying cardiac disease			
Non-user	1,597,962	5 (3.57)	-
Non-current user	607475	28 (4.61)	0.96 (0.55, 1.68)
Current user	373667	7 (1.87)	0.64 (0.27, 1.54)
Restrict data to 2000-2005			
Non-user	1324641	45 (3.4)	-
Non-current user	502092	22 (4.4)	0.80 (0.34, 1.88)
Current user	314664	6 (1.9)	0.44 (0.14, 1.40)
Cumulative ADHD med. use (< 1 yr, ≥ 1 year)			
Non-user	1,597,962	52 (3.25)	-
Non-current user	607475	26 (4.28)	0.98 (0.54, 1.76)
Current user: < 1 yr cumulative use	107447	3 (2.79)	1.03 (0.26, 4.17)
Current user: ≥ 1 yr cumulative use	266220	4 (1.50)	0.53 (0.19, 1.54)

4 Summary and Conclusions

4.1 Statistical Issues and Collective Evidence

Overall Findings

From the 2,579,104 patient years of follow-up there were 85 total serious cardiovascular events (3.30 events per 100,000 patient years); among non-users there were 52 events (3.25 events per 100,000 patient years), 7 events in current users (1.87 events per 100,000 patient years) and 26 events in non-current users (4.28 events per 100,000 patient years).

Among current users all the events occurred after one year in the study; cumulative ADHD medication exposure among these subjects ranged from 0.86 years to 6.82 years. Cumulative ADHD exposure among non-current subjects that had an event ranged from 0.04 years to 2.46 years; 7 of these subjects had a cumulative exposure exceed one year. Sixteen (16) of the 26 non-current events were remote users at the time of the event (365 days after last day of current use).

Most events occurred in the Tennessee Medicaid site (46, 5.93 events per 100,000 patient years). All events among current users occurred in the Medicaid sites (4 in Washington Medicaid and 3 in Tennessee Medicaid).

Among the incident users, there were 4 cardiovascular events in current users (2.08 events per 100,000 patient years) and 20 for non-current users (5.31 events per 100,000 patient years). The event rate was larger among the incident users (4.22 per 100,000 patient years) that ever used an ADHD medication (non-current and current users) compared to prevalent users (2.18 per 100,000 patient years).

Overall, the comparison of current users vs. non-users resulted in a HR of 0.67 and a 95% CI that included the null value (0.28, 1.64). The estimated HR comparing non-current users to non-users was approximately one. Among incident users, the estimated HR comparing current users to non-users was 0.67 with a 95% CI including one (0.22, 1.99). The estimated risk was slightly above one for non-current users compared to non-users with a 95% CI including one (HR=1.09; 95% CI = 0.59, 2.04).

Major Statistical Issues

The study design has the potential for generating biased risk estimates resulting from the inclusion of prevalent ADHD users into the sample. The specific bias that prevalent users may introduce include under ascertainment of events that occur early in therapy (prior to study entry) and the inability to control for disease risk factors that are altered by the drug therapy (Ray Am J of Epi, 2003; 159 (9)). The potential impact of this bias may be differential across sites and large since almost half (48.5%) of the ADHD users were prevalent users at baseline.

The broad study inclusion criteria resulted in two distinct study populations that may have systematic differences (some of which are not measured) that could confound the observed association of ADHD medication and serious cardiovascular disease.

Two PS model assumptions were violated. The first assumption violated, as a consequence of including prevalent users, was the PS model adjusted for post-treatment measurements. The second assumption, which is that each patient must have a true non-zero probability of receiving an ADHD medication, was violated due to the broad inclusion criteria for the non-user group. There were a sizable number of patients that would never have had a chance of receiving an ADHD medication. As demonstrated in the PS distribution plots, the distribution of PS among the non-users was near zero. In addition, the disparate PS distributions support the reviewer's concerns that non-users and current users differ with respect to patient characteristics.

Several protocol deviations were not mentioned in the final study report preventing a completed study evaluation. These deviations include the following:

- The primary study endpoint analyzed differed from the protocol specified endpoint.
- The primary statistical analysis using propensity scores and Cox regression were not prespecified.
- Use of the Brenner method to describe the non-user sample was not prespecified nor justified as an appropriate method in the results.

The final report lacks an adequate description of the sample, including how many and how often patients switched user status, the number of prevalent users, a description of the events among patients who received an ADHD medication and potential biases relating to significant differences in baseline characteristics.

There was insufficient information to support the assumption that PS balanced measured baseline covariates. Instead, the study report describes results based on the Brenner method, which as used is statistically inadequate to support the conclusion of measured covariate balance.

The study report incorrectly interpreted non-user characteristics at baseline using the Brenner method. This flawed interpretation, coupled with the summary information in the study report regarding the unadjusted non-user and no description of the Brenner method, gives an incorrect conclusion that the sample of non-users and current-users are similar.

Sensitivity analyses performed to evaluate possible study design limitations are inadequate to evaluate the overall net contribution of design choices. The incident users analysis is the only credible analysis performed since it is not vulnerable to prevalent-user bias. However, no results or discussion of pertinent and necessary diagnostics to evaluate the analyses were included in the study report.

There is evidence of heterogeneous risk across PS deciles. In the current user group all cardiovascular events occurred exclusively in the high deciles (7 through 10). Among non-users cardiovascular events were more concentrated in the lower deciles.

4.2 Conclusion and Recommendations

Concerns have been raised that the medication used to manage ADHD is associated with an increase in CV adverse events. To investigate this possible association, FDA and AHRQ co-funded separate studies in children and adults using multiple healthcare databases. On April 29, 2011 the child study final report was submitted to FDA.

Beyond data quality limitations inherent in investigations that use healthcare databases, the study design has limitations resulting from the inclusion of prevalent ADHD users in the sample. In addition, the broad patient inclusion criteria, which did not require a diagnosis of ADHD, resulted in a non-user comparison group that 1) may not yield clinically relevant comparisons since a sizable number of non-users would likely not receive an ADHD medication, 2) is characteristically different from the ADHD medication user groups, and 3) may have resulted in differential coding since it is more likely that a user was more recently treated (and possibly more frequently) by a health care provider than a non-user.

The final reports lacks in sufficient detail required to fully evaluate the study results. Lacking detail includes a lack of statistical diagnostics, and an inadequate description of the study sample and events. Additional limitations include 1) major protocol deviations are not discussed in the final study report, 2) insufficient information provided to support balance of baseline covariates using PS, and 3) incorrect interpretation of cohort characteristics of non-users at baseline and no unadjusted summaries of the non-user sample at baseline.

The incident user sensitivity analysis is considered the most credible analysis since it is not vulnerable to prevalent user bias. However, the results can not be fully evaluated since pertinent diagnostics and sample description were not provided or discussed in the final report.

Event rates appear to be heterogeneous across study sites. Most of the differences are driven by data from the public sites, particularly the Tennessee Medicaid site, compared to the private healthcare sites.

In conclusion, study findings that the estimated cardiovascular risks were lower in current users compared to non-users of ADHD medication have to be interpreted within the confines of the study limitations and the sub-optimal data-streams. Given the deficiencies associated with the study design and analysis, and an inadequate study report, it is recommended that 1) no comparative conclusions be drawn from the analyses provided, and 2) only results from the incident user incidence rates should be considered but with caution given the lack of detail in the final study report. In addition, the low rate of cardiovascular events among patients that received an ADHD medication is a useful finding despite concerns regarding lack of valid comparisons with non-users.

5 Appendix

5.1 Revised Tables for Final Study Report

This section displays three updated study tables for the final study report provided by the principal investigator after four incorrectly classified strokes events were removed. This error was first communicated to FDA July 1, 2011, and the revised Tables were provided to FDA August 11, 2011. Table numbers are same as used in the final study report.

Table 3. Occurrence of serious cardiovascular disease by current use of ADHD medications

ADHD medication use*	Person-years	Events	Rate/100,000	Hazard Ratio†	95% confidence interval low	95% confidence interval high
Non-user	1,597,962	49	3.07	1.00	Ref	Ref
Non-current user (former/indeterminate)	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
Methylphenidate	192,257	4	2.08	0.96	0.31	2.97
Amphetamines	137,448	1	0.73	---	---	---
Atomoxetine	29,330	1	3.41	---	---	---
Pemoline	14,632	1	6.83	---	---	---

*Current use included the period between the date of the prescription filling and the end of the days supply. Non-current use included indeterminate use (beginning the day after current use and lasting 89 more days) and former use (beginning 90 days after current use ended).

†Hazard ratios estimated with Cox regression models which included 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, and calendar year. Regression models were not fit for amphetamines, atomoxetine, and pemoline because there was only one event per medication class.

Table 4. Occurrence of individual endpoints by current use of ADHD medications

ADHD medication use*	Person-years	Events	Rate/100,000	Hazard Ratio†	95% confidence interval low	95% confidence interval high
Sudden Cardiac Death						
Non-user	1,597,962	17	1.1	1.00	Ref	Ref
Non-current user	607,475	13	2.1	1.52	0.65	3.57
Current User	373,667	3	0.8	0.88	0.23	3.34
Acute Myocardial Infarction†						
Non-user	1,597,962	6	0.4	1.00	Ref	Ref
Non-current user	607,475	3	0.5	-	-	-
Current User	373,667	0	0	-	-	-
Stroke						
Non-user	1,597,962	26	1.6	1.00	Ref	Ref
Non-current user	607,475	9	1.5	0.80	0.33	1.96
Current User	373,667	4	1.1	0.93	0.29	2.97

*Current use included the period between the date of the prescription filling and the end of the days supply. Non-current use included indeterminate use (beginning the day after current use and lasting 89 more days) and former use (beginning 90 days after current use ended).

†Hazard ratios estimated with Cox regression models which included 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, and calendar year. Because there were no events in the current user group, models were not calculated for acute myocardial infarction.

Table 5. Alternative Analyses, Adjusted Hazard Ratios for Serious Cardiovascular Events, According to Use or Nonuse of ADHD Medications.

Analysis	Exposure*	Reference	Hazard Ratio†	95% Confidence Interval
Primary Analysis	Current User	Nonuser	0.75	0.31-1.85
Reference category was former users of ADHD medications	Current User	Former User	0.70	0.29-1.72
Exposures were restricted to new ADHD medication users§	Incident User	Nonuser	0.73	0.24-2.10
Cases included those with severe underlying cardiac disease	Current User	Nonuser	0.71	0.29-1.72
Stratified by age <18 years and age 18-24 years	Current User	Nonuser	0.75	0.30-1.87

**Current use included the period between the date of the prescription filling and the end of the days supply. Former use included subsequent person-time that was not classified as current use.*

†Hazard ratios estimated with Cox regression models which included 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, and calendar year.

§Incident users included individuals who had no ADHD medication use in the 365 days prior to t_0.

5.2 Site-Specific Cohort Characteristics

Table 10. Adjusted and unadjusted cohort characteristic at baseline for Tennessee Medicaid

	Non-User		Current User
Covariate	**Unadjusted†**	**Brenner**	**Unadjusted**
Age (yrs)	8.7	8.8	8.7
male	70.1%	70.9%	70.1%
nonwhite	45.8%	26.1%	29.8%
SMSA-metro	67.6%	62.2%	63.7%
uninsured	24.7%	21.1%	23.0%
major depression	1.5%	10.0%	9.4%
bipolar	0.2%	2.0%	2.2%
psychosis	0.1%	1.1%	1.0%
autism	0.2%	1.0%	0.9%
mental retardation	0.9%	5.9%	5.4%
severe mental retardation	0.0%	0.1%	0.1%
suicide attempt	0.1%	0.4%	0.4%
any antidepressant	2.0%	16.5%	17.5%
mood stabilizers	0.6%	4.5%	4.8%
any antipsychotic	0.6%	6.0%	7.3%
benzodiazepines (w/ anxiety dx)	0.1%	0.5%	0.4%
psychiatric hospitalization	0.4%	3.3%	3.2%
smoking	0.9%	1.6%	1.4%
alcohol abuse	0.1%	0.5%	0.4%
cocaine abuse	0.0%	0.1%	0.1%
opiate abuse	0.0%	0.1%	0.1%
other substance abuse	0.3%	1.2%	1.1%
obesity	0.8%	1.4%	1.3%
major CV disease	1.5%	2.2%	2.0%
diabetes	0.4%	0.9%	0.7%
poorly controlled diabetes	0.1%	0.2%	0.2%
minor CV disease	4.1%	8.0%	7.5%
CV hospitalization	0.3%	0.5%	0.4%
CV ED visit	0.8%	1.4%	1.3%
asthma	19.4%	31.1%	27.6%
seizures	1.1%	4.4%	3.6%
life-threatening chronic disorders	0.8%	1.8%	1.4%
other hospitalizations	4.3%	8.2%	7.5%
other ED visits	27.8%	37.4%	35.9%
psychiatric outpatient visit	6.7%	54.3%	59.0%
CV outpatient visits	5.4%	9.3%	8.4%
other outpatient visits	79.1%	95.9%	95.4%
any other rx	22.9%	37.9%	33.8%

† Page 14-17 from response to FDA information request received 1/15/2011

Table 11. Adjusted and unadjusted cohort characteristic at baseline for Kaiser Permanente

	Non-user		Current User
Covariate	**Unadjusted†**	**Brenner**	**Unadjusted**
age (yrs)	11.1	11.2	11.1
male	73.9%	74.0%	74.0%
nonwhite	70.2%	50.0%	56.4%
SMSA-metro	95.3%	95.9%	95.6%
major depression	1.3%	13.3%	11.6%
bipolar	0.1%	1.7%	1.7%
psychosis	0.1%	0.6%	0.4%
autism	0.2%	2.3%	2.5%
mental retardation	0.3%	1.2%	2.1%
severe mental retardation	0.0%	0.0%	0.0%
suicide attempt	0.0%	0.3%	0.2%
any antidepressant	1.2%	17.8%	14.7%
mood stabilizers	0.3%	3.4%	3.4%
any antipsychotic	0.3%	4.4%	4.5%
benzodiazepines (w/ anxiety dx)	0.1%	0.4%	0.3%
psychiatric hospitalization	0.2%	2.1%	1.5%
smoking	0.4%	1.6%	1.2%
alcohol abuse	0.2%	0.9%	0.8%
cocaine abuse	0.0%	0.1%	0.1%
opiate abuse	0.0%	0.1%	0.1%
other substance abuse	0.3%	1.5%	1.5%
obesity	2.2%	3.4%	3.1%
major CV disease	0.5%	0.9%	0.8%
diabetes	0.2%	0.3%	0.2%
poorly controlled diabetes	0.0%	0.1%	0.1%
minor CV disease	1.8%	4.3%	3.8%
CV hospitalization	0.2%	0.4%	0.3%
CV ED visit	0.2%	0.3%	0.3%
asthma	16.0%	24.8%	21.1%
seizures	0.3%	1.3%	1.1%
life-threatening chronic disorders	0.6%	1.2%	0.9%
other hospitalizations	1.9%	4.0%	3.3%
other ED visits	9.0%	14.1%	12.4%
psychiatric outpatient visit	3.8%	57.4%	67.9%
CV outpatient visits	1.9%	3.5%	2.8%
other outpatient visits	71.3%	93.7%	91.8%
any other medication	17.3%	28.1%	24.7%
KPSC	40.5%	37.1%	40.7%

† Page 14-17 from response to FDA information request received 1/15/2011

Table 12. Adjusted and unadjusted cohort characteristic at baseline for Ingenix i3

	Non-user		Current User
Covariate	**Unadjusted**	**Brenner**	**Unadjusted**
age (yrs)	12	12.5	12
male	70.2%	69.5%	70.3%
major depression	1.8%	12.4%	11.1%
bipolar	0.2%	1.9%	2.2%
psychosis	0.1%	0.5%	0.4%
autism	0.2%	1.0%	1.2%
mental retardation	0.6%	2.3%	4.2%
severe mental retardation	0.0%	0.0%	0.0%
suicide attempt	0.1%	0.3%	0.3%
any antidepressant	1.8%	17.2%	13.8%
mood stabilizers	0.5%	3.9%	4.1%
any antipsychotic	0.3%	3.7%	4.8%
benzodiazepines (w/ anxiety diagnosis)	0.1%	0.7%	0.6%
psychiatric hospitalization	0.2%	1.9%	1.7%
smoking	0.5%	1.0%	0.8%
alcohol abuse	0.2%	0.5%	0.6%
cocaine abuse	0.0%	0.1%	0.1%
opiate abuse	0.0%	0.1%	0.1%
other substance abuse	0.3%	0.9%	1.0%
obesity	0.6%	0.8%	0.8%
major CV disease	0.2%	0.5%	0.5%
diabetes	0.4%	0.5%	0.5%
poorly controlled diabetes	0.2%	0.2%	0.2%
minor CV disease	4.2%	8.1%	7.6%
CV hospitalization	0.1%	0.2%	0.2%
CV ED visit	0.3%	0.3%	0.3%
asthma	15.9%	26.5%	21.4%
seizures	0.5%	2.3%	1.9%
life-threatening chronic disorders	1.0%	1.8%	1.5%
other hospitalizations	1.3%	2.4%	2.2%
other ED visits	8.3%	9.6%	9.3%
psychiatric outpatient visit	5.3%	55.5%	63.7%
CV outpatient visits	4.4%	7.1%	6.5%
other outpatient visits	75.0%	92.8%	92.8%
any other medication	24.4%	40.5%	34.4%

† Page 14-17 from response to FDA information request received 1/15/2011

Table 13. Adjusted and unadjusted cohort characteristic at baseline for Washington Medicaid

	Non-user		Current User
Covariate	**Unadjusted†**	**Brenner+**	**Unadjusted†**
age (yrs)	10	-	10
male	72.2%	-	72.4%
nonwhite	25.3%	-	16.5%
SMSA-metro	68.9%	-	69.4%
major depression	1.4%	-	6.0%
bipolar	0.2%	-	1.8%
psychosis	0.2%	-	0.6%
autism	0.3%	-	1.2%
mental retardation	0.7%	-	3.6%
severe mental retardation	0.0%	-	0.0%
suicide attempt	0.0%	-	0.1%
any antidepressant	2.6%	-	18.5%
mood stabilizers	0.7%	-	5.6%
any antipsychotic	0.7%	-	5.6%
benzodiazepines (w/ anxiety dx)	0.1%	-	0.2%
psychiatric hospitalization	0.4%	-	2.1%
smoking	0.6%	-	0.7%
alcohol abuse	0.6%	-	1.2%
cocaine abuse	0.0%	-	0.0%
opiate abuse	0.0%	-	0.1%
other substance abuse	0.6%	-	1.4%
obesity	0.3%	-	0.5%
major CV disease	0.2%	-	0.4%
diabetes	0.3%	-	0.5%
poorly controlled diabetes	0.1%	-	0.2%
minor CV disease	2.6%	-	6.5%
CV hospitalization	0.2%	-	0.3%
CV ED visit	0.8%	-	1.0%
asthma	11.9%	-	18.4%
seizures	0.8%	-	2.1%
life-threatening chronic disorders	0.7%	-	1.1%
other hospitalizations	7.3%	-	10.7%
other ED visits	20.8%	-	26.1%
psychiatric outpatient visit	5.9%	-	58.7%
CV outpatient visits	2.7%	-	4.3%
other outpatient visits	74.6%	-	91.2%
any other medication	13.8%	-	23.5%

† Unadjusted estimates from page 14-17 of response to FDA information request received 1/15/2011
+ Brenner method estimates not provided in final report

5.3 Site-Specific Propensity Score Distributions

Figure 3. Tennessee Medicaid: propensity score distribution for current and non-current users

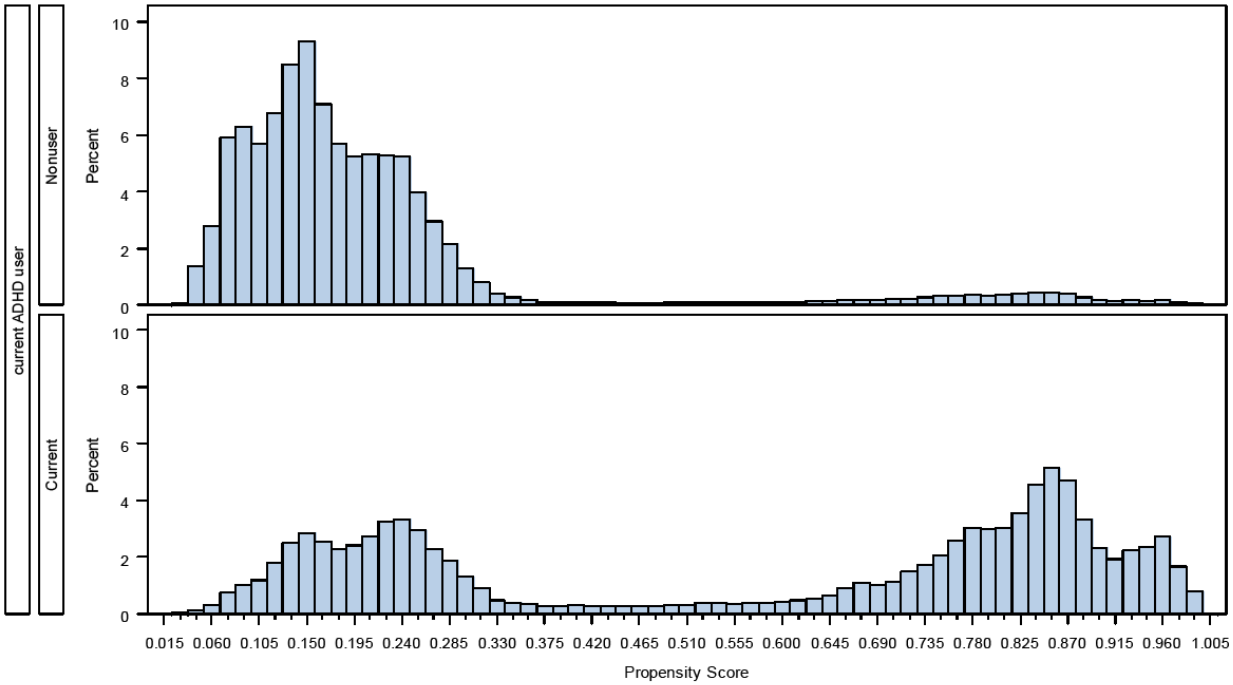


Figure 4. Kaiser Permanente: propensity score distribution for current and non-current users

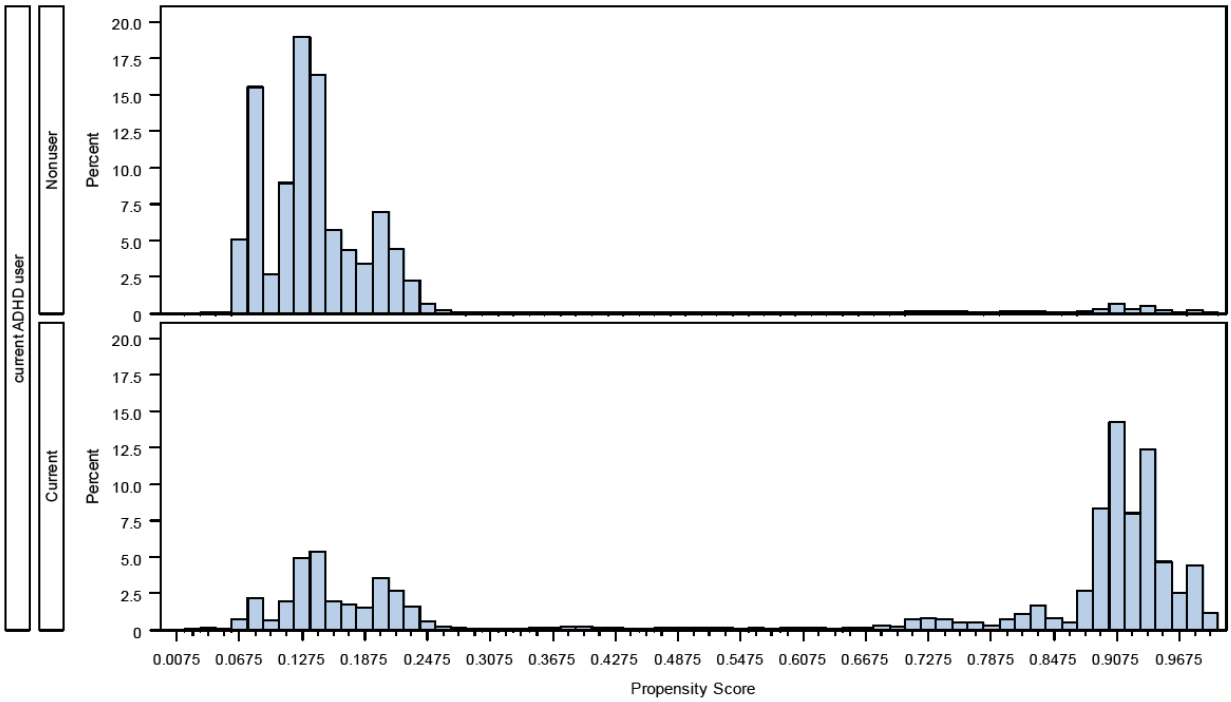


Figure 5. Ingenix i3: propensity score distribution for current and non-current users

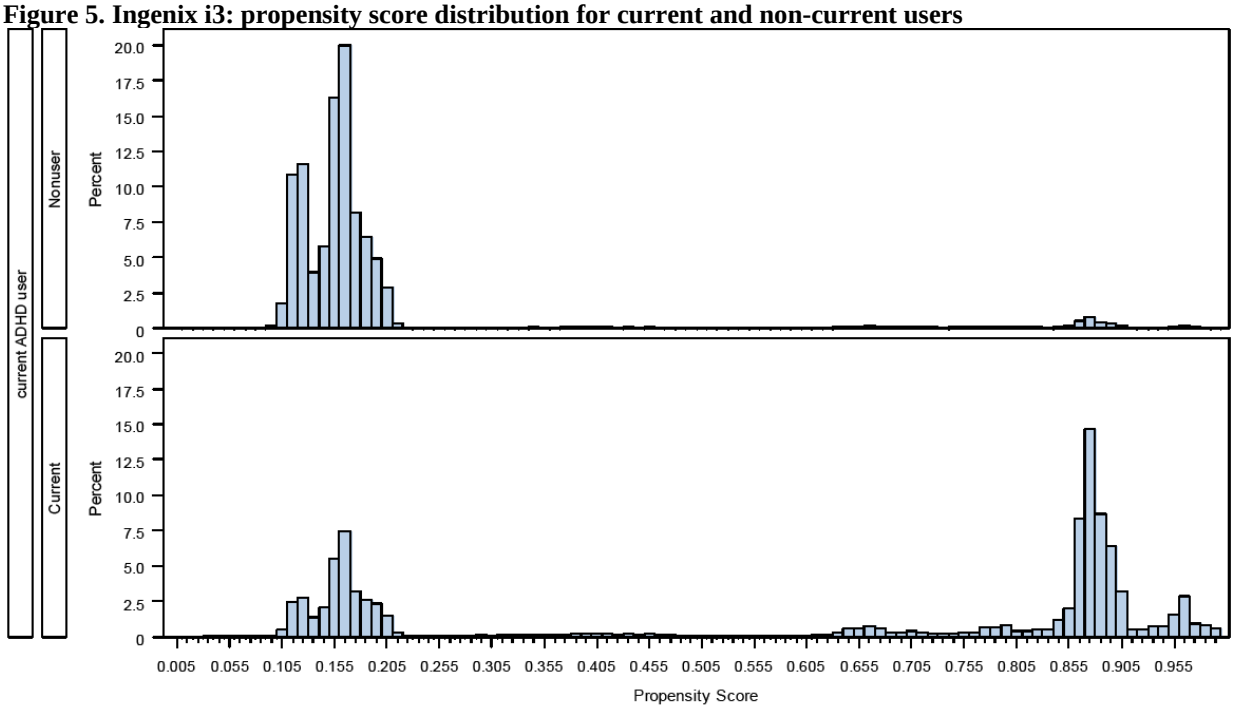
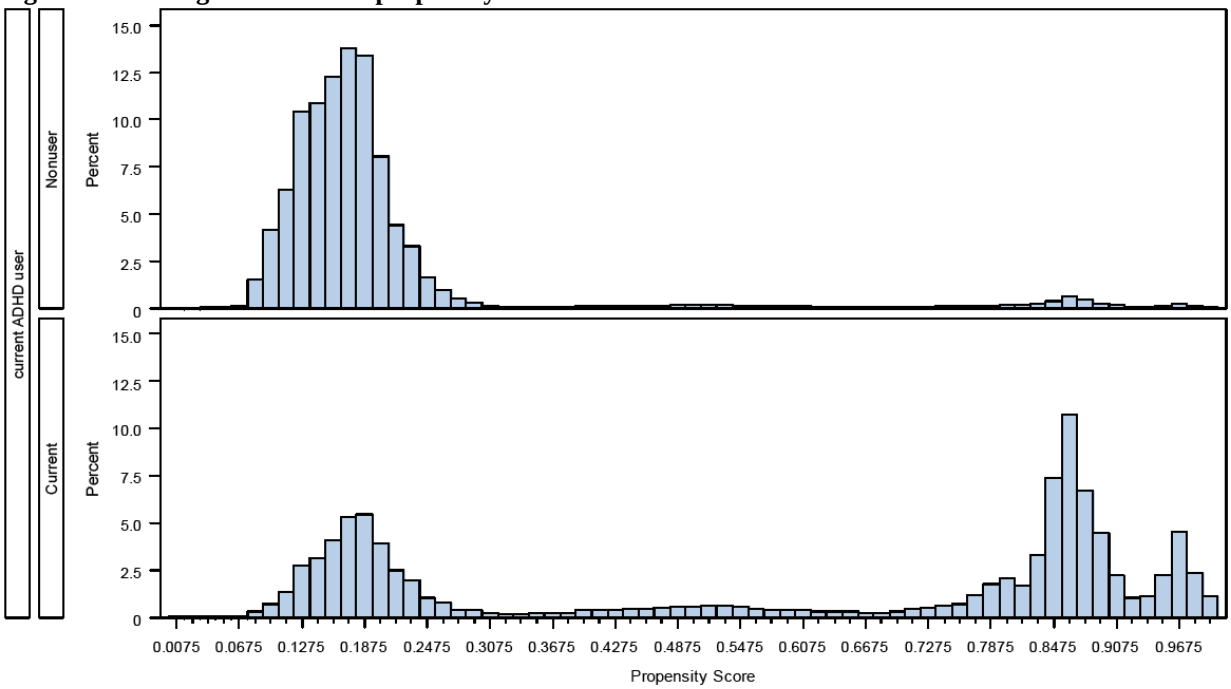


Figure 6. Washington Medicaid: propensity score distribution for current and non-current users



5.4 Events and Event Rates by PS Deciles

Table 14. Event counts and rates by user status and PS decile by site

Site	Decile	Non Users n (rate/100,000 py)	Non-Current Users n (rate/100,000 py)	Current Users n (rate/100,000 py)
TN Medicaid	1	6 (10.36)	1 (22.61)	0 (0.00)
	2	3 (6.11)	1 (16.91)	0 0.00)
	3	2 (3.12)	2 (19.07)	0 0.00)
	4	3 (4.49)	1 (8.11)	0(0.00)
	5	6 (10.11)	3 (23.79)	0 (0.00)
	6	4 (7.06)	3 (17.54)	0 0.00)
	7	2 (3.20)	0 (0.00)	1(12.99)
	8	2 (5.61)	1 (2.69)	2 16.01)
	9	0 (0.00)	0 (0.00)	0 0.00)
	10	1 (12.59)	2 (3.46)	0 (0.00)
WA Medicaid	1	1 (5.10)	0 (0.00)	0 0.00)
	2	0 (0.00)	0 (0.00)	0(0.00)
	3	0 (0.00)	0 (0.00)	0 (0.00)
	4	0 (0.00)	0 (0.00)	0 (0.00)
	5	0 (0.00)	0 (0.00)	0 (0.00)
	6	0 (0.00)	0 (0.00)	0 (0.00)
	7	1 (5.32)	0 (0.00)	0 (0.00)
	8	0 (0.00)	0 (0.00)	2(27.71)
	9	0 (0.00)	2 (14.90)	0(0.00)
	10	0 (0.00)	1 (8.10)	2(16.21)
Kaiser Permanente	1	1 (2.26)	0 (0.00)	0(0.00)
	2	1 (1.87)	0 (0.00)	0(0.00)
	3	2 (4.10)	1 (23.44)	0(0.00)
	4	0 (0.00)	0 (0.00)	0(0.00)
	5	0 (0.00)	0 (0.00)	0(0.00)
	6	4 (6.90)	0 (0.00)	0(0.00)
	7	0 (0.00)	0 (0.00)	0(0.00)
	8	1 (4.73)	0 (0.00)	0(0.00)
	9	1 (32.52)	0 (0.00)	0 (0.00)
	10	0 (0.00)	3 (12.05)	0(0.00)
Ingenix i3	1	1 (1.37)	0 (0.00)	0(0.00)
	2	1 (1.06)	0 (0.00)	0(0.00)
	3	0 (0.00)	0 (0.00)	0(0.00)
	4	0 (0.00)	0 (0.00)	0(0.00)
	5	2 (2.07)	1 (7.13)	0(0.00)
	6	3 (3.19)	0 (0.00)	0(0.00)
	7	1 (1.26)	1 (7.57)	0(0.00)
	8	3 (6.64)	1 (2.71)	0(0.00)
	9	0 (0.00)	1 (1.83)	0(0.00)
	10	0 (0.00)	1 (1.86)	0(0.00)

Table 15. Event counts and rates by user status and PS decile pooled across sites

Decile	Non Users n (rate/100,000 py)	Non-Current Users n (rate/100,000 py)	Current Users n (rate/100,000 py)
1	9 (4.62)	1 (6.26)	0 (0.00)
2	5 (2.32)	1 (4.52)	0 (0.00)
3	4 (1.96)	3 (11.07)	0 (0.00)
4	3 (1.52)	1 (3.47)	0 (0.00)
5	8 (3.80)	4 (12.17)	0 (0.00)
6	11 (4.87)	3 (7.08)	0 (0.00)
7	4 (2.08)	1 (2.17)	1 (4.20)
8	6 (5.46)	2 (1.91)	4 (6.53)
9	1 (3.96)	3 (2.16)	0 (0.00)
10	1 (4.57)	7 (4.70)	2 (1.90)

5.5 Additional Comments on the Brenner Method

In this section we show that the similarity of the Brenner adjusted estimates does not imply stratum specific balance of baseline variables. Consider the hypothetical stratum-specific estimates and weights shown in Table 16 below. In this example, the unadjusted estimate for Group 1 is 0 and -0.5 for Group 2. When the stratum specific estimates for Group 2 are weighted based on the distribution of patients in Group 1, the adjusted estimate for Group 2 (i.e., Brenner estimate) is 0, which is the same as the unadjusted estimate for Group 1. Therefore, despite the stratum specific estimates being unequal between groups, the adjusted estimate is the same. Due to this factor associated with this model, without evaluating stratum specific estimates one can not conclude covariate balance by comparing the Brenner adjusted estimate.

Table 16. Hypothetical example of Brenner Method

	Strata specific estimate		Proportion of total sample	
Strata	Group 1	Group 2	Group 1	Group 2
1	**0**	**-2**	**1/3**	**2/4**
2	**0**	**1**	**1/3**	**1/4**
3	**0**	**1**	**1/3**	**1/4**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRADLEY W MCEVOY
09/28/2011

LAREE A TRACY
09/28/2011

MARK S LEVENSON
09/28/2011