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

ADDENDUM

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 (date 10/25/2011) for Observational Study: Attention Deficit Hyperactivity Disorder Medications and Risk of Serious Cardiovascular Disease in Children and Youth
Date(s):	Statistical review: 9/29/2011 Addendum to statistical review: 11/03/2011
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Keywords: Observational study, propensity scores, ADHD medications, sudden cardiac death, stroke, myocardial infarction, outcome study, pediatrics

This addendum updates the September 28, 2011 statistical review (statistical reviewer: Dr. Bradley McEvoy) of the original study report (received April 29, 2011) with updated content presented in a revised final study report that was received October 31, 2011 (document date: October 25, 2011). The basis for the update was to correct study results based on four (4) outcome events of transient ischemic attacks (TIA) that were erroneously classified as strokes in the previous report. In addition to the updated total number of events, there were several other revisions, which are outlined in this addendum summary along with key differences between the two reports and their impact on the statistical evaluation.

The misclassified stroke events were communicated to FDA on July 1, 2011; however, the revised report was not submitted until 10/31/2011. In the 4/29/2011 report, total stroke events were 29, 10 and 4 in the nonuser, former user and current user groups respectively. The updated stroke events in the 10/25/2011 report are 26, 9 and 4 in the nonuser, former user and current user groups respectively. Total events changed from 52, 26 and 7 to 49, 25 and 7 in nonuser, former user and current user groups respectively (Table 1). The updated rates are also presented by specific event in the original statistical review in Appendix 5, section 5.1.

Table 1: Occurrence of serious cardiovascular disease by use of ADHD medication (10/25/2011)

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
Former 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

*Updated events as reported in Table 3 of the 10/25/2011 revised study report

In the 10/25/2011 final report, cohort characteristics by baseline ADHD medication (Table 2 in the report) are adjusted by age, sex and site. In contrast, these characteristics are presented as adjusted results according to the Brenner method in the 4/29/2011 report. The statistical reviewer expressed several key concerns in the original review regarding use of the Brenner method; however, given the elimination of this approach when describing cohort characteristics in the final report, the new material is deemed acceptable. Concerns remain; however, regarding the initial use of the Brenner method and the original conclusions drawn from this using this approach.

The 10/25/2011 revised report no longer presents propensity score histograms by user status at baseline (refer to the original statistical review, Figures 3-6). The statistical reviewer considers this a major omission since the plots illustrate key differences at baseline among the user groups. The 10/25/2011 report retains the site specific Brenner adjusted estimates (Appendix 6) as an attempt to the show propensity scores were able to balance baseline covariates. As noted in the original statistical review, the statistical reviewer considers this information insufficient to demonstrate balance among groups with respect to measured covariates and is also limited since the approach is inconsistent with the

outcome analysis. In addition, the revised report is lacking in important diagnostic information pertaining to the preferred incident user analysis.

The revised 10/25/2011 report presents unadjusted risk summaries by site (Appendix 12) whereas the 4/29/2011 report presents adjusted risk estimates (statistical review, Table 8). The 10/25/2011 report no longer presents adjusted risk estimates over concerns with few events. In addition, the 10/25/2011 report now discusses the potential for an interaction between ADHD medication use Medicaid sites. However, the conclusion that there is an absence of heterogeneity based on the lack of overlap in 95% confidence intervals is not a supported statement. This conclusion needs to be supported by a formal test for interaction rather than qualitative interpretation of confidence intervals. This was communicated to the authors on 10/26/2011 based on an excerpt from the draft manuscript.

The 10/25/2011 revised report omits results from certain sensitivity analyses that were included in the 4/29/2011 report. Sensitivity analyses excluded were carryover user status at re-entry, adjustment using individual covariates, restricted data from 2000-2005, controlling for psychiatry utilization, and time dependent variables fixed at baseline.

In addition, the 10/25/2011 report now presents results from analyses by age group (2-17 and 18-24, Table A.11.3). The description of results from the analysis of children age 2-17 in the report is ambiguous and can potentially be misinterpreted. Specifically, the final report states “in analyses including only children 2-17 years of age, no association was found between ADHD medication use and serious cardiovascular events (HR 0.98; 95% CI 0.41-2.36)”. To avoid possible misinterpretation of the results, it has to be noted that the subgroups only pertain to age at baseline. Events and exposure that occurred after patients exceeded the age limit defined by the age subgroup were not censored. For instance, in the 2-17 years age grouping 3 of the 7 cardiovascular events among current users were older than 17 years when they experienced the event[1].

[1] Source—Supplemental material of case descriptions submitted 2/23/2011 by the principal investigator to FDA.

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