Reviewer's report

Title: Do Prescription Stimulants Increase the Risk of Adverse Cardiovascular Events?: A Systematic Review

Version: 2 Date: 8 November 2011

Reviewer: Sean Hennessy

Reviewer's report:

Major Compulsory Revisions

1. In addition to PUBMED and MedLine, is there a reason not to search EMBASE and Google Scholar as well?

2. Because of the timing of when this review was done, information on the safety of stimulants is in rapid flux. For example, the results in children of the study led by Cooper and Ray of this topic were published in NEJM on Nov 1, 2011. It seems likely that the adults paper from this group will be published soon, as will the adult results of the study led by Schelleman and Hennessy. The adult results of the Schelleman/Hennessy paper were presented in abstract form in 2011 abstract issue of Pharmacoepidemiology and Drug Safety. There is another study led by Almut Winterstein that is underway:

3. Were abstracts of studies identified? If not, the rationale for this should be provided.

4. Please provide the rationale for excluding non-English papers. I believe that prior work has shown that 'negative' papers are more likely than 'positive' papers to be published in English.

5. Confounding: "Use of propensity scoring and instrumental variables offers the promise of adjusting for selection biases, and we submit that future studies of prescription stimulant use and cardiovascular outcomes should employ these techniques." Propensity scores allow one to adjust for *measured* confounders when there are many confounders and few outcomes. It does not adjust for unmeasured factors, and does not adjust for selection bias. Instrumental variable methods adjust for measured and unmeasured confounders, provided that the underlying assumptions are met. However, a good instrumental variable has not been identified for this application.

6. Was anything done to examine the reliability of abstraction of information from published papers?

Minor Essential Revisions

None
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I am an investigator of a study, funded by Shire, of the cardiovascular safety of ADHD medications.

I have served as a consultant to several pharmaceutical companies, although none of that consulting has related to ADHD medications.