Author's response to reviews

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

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Author's response to reviews: see over
Dear Editors,

We hereby submit a revision of our manuscript “Do Prescription Stimulants Increase the Risk of Adverse Cardiovascular Events?: A Systematic Review.” Two very important studies were published since our original manuscript was reviewed. These studies by Cooper et al. (New England Journal of Medicine, 2011) and Habel et al. (JAMA, 2011) have necessitated a very broad reworking of this review. The results, discussion, and conclusions have been significantly modified. We summarize the changes below, along with responses to the suggestions made in the very helpful reviews. As a result of the addition of the Habel et al. and Cooper et al. studies, we believe that this review is now much improved and will be of greater interest to readers. Our response to reviewers is attached below.

Sincerely,

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Response to Reviewers

1. A reviewer suggested that additional databases be queried, specifically EMBASE and Google Scholar. Additional database searches were conducted using EMBASE and Google Scholar. An additional 181 abstracts were reviewed. As mentioned above, two additional studies were included in the systematic review, and the results and discussion were updated to reflect these additional studies (Cooper et al. and Habel et al.).
   a. Figure 2 (study flowchart) was updated.
   b. Abstract was updated to reflect changes in the manuscript.
   c. Results section describing the study search was updated (page 7).
   d. Cooper and Habel studies were described in Results section (page 8-10).
   e. At the beginning of the Discussion, the limitations of the Habel study were described (pages 15-16).
   f. Conclusions paragraph in Discussion replaced based on updated synthesis as a result of the Cooper and Habel studies (page 20).
   g. Table 1 updated to include Cooper and Habel studies.
2. Based on reviewer suggestion, the introduction was significantly reduced.
   a. Details on the increase of prescription stimulant use were referenced rather than described in detail (page 4).
   b. The discussion about indications for stimulants was deleted.
3. Based on reviewer suggestion, language in the introduction was changed so as to not be so US-centric. A reference on Canadian policy was present in the first draft. We added a reference to Australian policy as well (page 4-5).
4. In the introduction, the examples of sibutramine and Qnexa are now nearer to the beginning of the manuscript as was suggested by the reviewer (page 5).

5. EMBASE and Google Scholar searches were not limited to English, thus we have removed the phrase “published in English.” However, our search did not yield a non-English study that necessitated full-text review. Nor did we find any non-English studies in searching references.

6. We added a sentence to describe why most records were excluded on the basis of titles and abstracts: “due to not being topical to prescription stimulants and not having appropriate endpoints” (page 7).

7. As suggested, we shortened the paragraph about hard clinical outcomes in the discussion (page 17).

8. In the original manuscript we had a summary section in the results where we synthesized the reviewed studies. This has been moved to the beginning of the discussion section (page 15).

9. In regards to propensity scoring, the reviewer says “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.” While this is a commonly held belief, we have a slightly different take. Our view is best summarized by Stukel et al. (2007; JAMA 297(3):278-285): “Propensity scores cannot remove hidden biases except to the extent that unmeasured prognostic variables are correlated with the measured covariates used to compute the score.” A classic example of this is a home zip code (urban vs. rural), which could correlate with access to healthcare. We do agree with the reviewer that an instrumental variable is generally the better tool to account for unmeasured confounders. As such, a sentence in the original manuscript that said “Only the Holick et al. study addressed the problem of differences in stimulant-using and non-using populations (i.e. selection bias)” has been deleted (was on page 10 in the original manuscript).

10. As the reviewer suggested, we have clarified our recommendations regarding the role of clinical trials. The sentence in the conclusion (page 20) suggesting that there is a role for clinical trials was removed. Additionally in the discussion under the heading “Low Absolute Rates of Cardiovascular Events” (page 16) the following sentence was deleted: “RCTs will not be the best way to answer this question.”.

11. In the “Study Populations” paragraph in the Discussion, we make mention of the need to study the elderly population, 65 years and older (page 17).

12. As suggested, I have searched for the pending Winterstein study, but have not been able to locate it. Our understanding is that it is not yet published, so it is not eligible for inclusion in the review.

13. The reviewer asks: “Why do stimulants increase blood pressure, induce vasospasms, vasculitis and arrhythmia. Only stating that they do cause events seems unsufficient.”
   a. Regarding blood pressure, have added the following: “Stimulants act by blocking reuptake of norepinephrine and dopamine as well as increasing their release into the extracellular space. Stimulant-induced blood pressure increases may be mediated by central dopaminergic effects and dopamine-induced increases in peripherally circulating epinephrine” (page 11).
   b. Our statement regarding vasculitis provides a potential explanation as to how it is mediated: “formation of circulating proinflammatory immunoactive advanced glycation end products that may mediate vasculitis” (page 11).
   c. Regarding arrhythmias, have added the following sentence: “Prolongation of the QT interval has been associated with a potentially fatal polymorphic ventricular tachycardia called torsades de pointes” (page 11).
d. Regarding vasospasm, added the following sentence: “Stimulant-induced vasospasm may be caused by increased levels of circulating catecholamines” (page 11).

14. The reviewer asks: “Why are the studies on medical and nonmedical use described in this section not included in the systematic review?” We reported on case reports, cases series, observational studies, and clinical trials that pertained to the question of whether stimulants can cause adverse cardiovascular events. But these studies did not fit our inclusion criteria to be included in the systematic review. Only eight studies fit our inclusion criteria.

15. Fixed typos in Figure 1 (Conceptual Model).

16. Note, what was Figure 1 in the original submission is now Figure 2, and vice versa, as their order of introduction in the manuscript has been reversed.