Author's response to reviews

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

Authors:

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

Our responses to the reviewers’ comments are written below. Extensive changes were made to the manuscript in response to the very helpful comments by the reviewers. In summary, those changes were 1) to remove the “critical review” portion of the manuscript that was not directly applicable to the systematic review, 2) to include two new studies published in 2012, and 3) to reduce the size of the manuscript. In our opinion, the resulting manuscript is much more concise and thematically consistent.

We hope that the revised manuscript will meet the reviewers’ and editors’ expectations and prove of benefit to the journal’s readership should it be accepted for publication.

Sincerely,

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RESPONSE TO REVIEWERS

Reviewer Peters

Reviewer: “The abstract requires some textual revision as sentences are not smoothly written and as the results section includes references which is unusual for abstracts.”

Response: The abstract was revised. It was edited for clarity. Specific references in the results section were removed. The section on the critical review (which was not retained in the paper) was removed. The abstract was revised to reflect manuscripts in the revision, specifically the addition of two papers to the systematic review. The length was reduced from 336 words to 301 words.

Reviewer: “Also, the conclusion [in the abstract] does not reflect the result from the study but is rather a recommendation for future studies. Which conclusions can be drawn from the present investigation?”
Response: The conclusion was rewritten to reflect the substantive conclusions of the paper as found in the discussion section. Recommendations for future studies was reduced to a single short sentence.

Findings of an association between prescription stimulant use and adverse cardiovascular outcomes are mixed. Studies of children and adolescents suggest that statistical power is limited in available study populations, and the absolute risk of an event is low. More suggestive of a safety signal, studies of adults found an increased risk for transient ischemic attack and sudden death/ventricular arrhythmia. Accounting for confounding and selection biases in these studies is of particular concern. Future studies should address this and other methodological issues.

Reviewer: “However, a key issue which is not clearly described [in the introduction] is why stimulants are used at all. In the end of the introduction section, there is a hidden sentence saying that they are you to promote weight loss, but a clear rationale for the use of stimulants is required in the beginning of the introduction section.”

Response: In the second paragraph of the introduction, we have included a sentence that describes how prescription stimulants are used (page 4).

Prescription stimulants are primarily used in the treatment of attention deficit hyperactivity disorder (ADHD), but also for obesity [7] and narcolepsy [8] as well as “off-label” indications such as depression [9], stroke rehabilitation [10], and traumatic brain injury [11].

Reviewer: “There exist widely used checklists to assess the quality of observational studies. Was any of these used? Please check the Cochrane collaboration for their current recommendations.”

We have reviewed the Cochrane Collaboration’s recommendations (http://www.cochrane-handbook.org/) for assessment of studies. Recommendations are much more specific for randomized studies (Chapter 8) than for non-randomized studies (Chapter 13). The reviewer suggests the use of a checklist. It is worth mentioning that the Cochrane Collaboration does not recommend the use of checklists for even the evaluation of randomized studies: “The Collaboration’s recommended tool for assessing risk of bias is neither a scale nor a checklist. It is a domain-based evaluation, in which critical assessments are made separately for different domains” (Section 8.3.1).

Regarding the Collaboration’s specific recommendations for non-randomized studies, such as the ones that are included in this review, the recommendation is “to consider (a) the weaknesses of the designs that have been used (such as noting their potential to ascertain causality), (b) the execution of the studies through a careful assessment of their risk of bias, especially (c) the potential for selection bias and confounding to which all NRS are suspect and (d) the potential for reporting biases, including selective reporting of outcomes” (Section 13.1.3). We would make the argument that our review does exactly those things. Furthermore, the Collaboration says “the variety of study designs classified as NRS [non-randomized studies], and their varying susceptibility to different biases, makes it difficult to produce a generic robust tool that can be used to evaluate risk of bias.” We agree that using a specific tool or checklist is very problematic. The Collaboration makes the point that “review authors require a deeper knowledge of epidemiology when assessing the risk of bias in [non-randomized studies], compared with randomized trials.” Both authors, in this case of this review, have received
specialized training in understanding the risk of bias—Dr. Halm has received a Masters degree in public health (MPH) and Dr. Westover has received a Masters degree in clinical sciences (MSCS).

In conclusion, our review has focus on the methodology of the included studies, with specific focus on study design, statistical power, confounding, and selection bias. Table 1, as written, contains information in that regard. The text of the manuscript contains further details. The difficult task in the case of this review is to efficiently and accurately communicate the strengths and limitations of the studies, given their disparate designs. We could certainly greatly expand our discussion of these studies in the review. One might be able to write an entire review (4000 words) on just the study by Habel et al. We have tried to balance the need for brevity and complete information in the review as it is written. We believe that this review directly addresses what the Cochrane Collaboration suggests should be addressed in a review of non-randomized studies.

Reviewer: “The results section is very lengthy. It is strongly recommended to just describe the results of each separate study without describing the limitations of each study very extensively. This may be done in the discussion section, or a table may be included describing the strengths and limitations of each study separately. Such overview would be much easier to interpret than the current lengthy description. Such table could be combined with a quality appraisal of each study as suggested above.”

Response: The results section has been decreased significantly. In the last submitted version, it was 1305 words. In this version it is now 1005 words. Limitations that were previously described in the results section are now described in the discussion section. We did not feel that a table format could easily or efficiently describe limitations of the studies, beyond what we have already included in the table. Thus, these limitations are described in the discussion, which we think is appropriate.

Reviewer: “The last sentence of the results section: 'Neither report by Habel and colleagues included data on individuals 65 years or older, who might be expected to be those at highest potential risk of adverse cardiac events.' should be moved to the discussion section and some references should be provided to support this hypothesis.”

Response: The aforementioned sentence was removed from the results section. To the discussion, we added a sentence (below, in bold italics) that describes how the vast majority of deaths due to stroke and myocardial infarction occur in the elderly (page 14).

While the recent Habel et al. study is a major advance filling what was a very large gap in the literature regarding cardiovascular safety of prescription stimulants in adults, it did not address adults 65 years and older. This group may be especially susceptible to the cardiovascular effects of prescription stimulants, as greater than 80% of deaths due to heart disease occur in those 65 years or older, and the death rate from stroke in persons 65-74 and 75-84 years old is approximately 8 times and 30 times greater, respectively, than in persons 45-54 years old [74].

In the first paragraph of the introduction, we give additional reasons why the elderly would be most at risk (page 4):
Older adults using prescription stimulants [4] may be particularly vulnerable to adverse cardiovascular events, given their higher background rate of cardiovascular events and comorbid conditions, higher doses of stimulants [2,5], and slower drug elimination [6].

Reviewer: However, not being an expert in the field, it is still difficult to understand the mechanisms through which stimulants act based on the description provided by the authors. As the paper is lengthy, it may be beneficial to make two papers out of it. One describing evidence on the potential mechanisms through which stimulants may increase cardiovascular disease risk followed by a paper describing the actual evidence on this issue. Such approach would probably result in two papers both having a clear message and would avoid multiple messages and aims which the current paper has.

Response: We agree with the reviewer that the review had become unwieldy and unfocused. Regarding mechanisms of action, the reviewer is correct, an entire review could be written on that topic. For the purpose of this review, we have elected to more acutely focus on the systematic review and the included observational studies. As such, we have removed almost all material related to the “critical review”, specifically the parts that focused on amphetamine substance use disorders and clinical trials of stimulants. The following changes were made in that regard:

1. The section “Published Clinical Reports Linking Medical Use of Stimulants to Cardiovascular Events” has been summarized into one sentence and moved to the introduction (page 4):

   Prescription stimulants have been linked to adverse cardiovascular events in case reports [24-26,35,46-49].

2. The descriptions of ephedra and phenylpropanolamine have been wholly deleted.
3. The section “Published Reports Linking Nonmedical Use of Stimulants to Cardiovascular Events” concerning nonmedical use of stimulants has been deleted.
4. The section “Safety Implications of Clinical Trials of Prescription Stimulants in the Treatment of Attention Deficit Hyperactivity Disorder” has been deleted.
5. The figure that was entitled “Conceptual Model of Prescription Stimulant-Associated Adverse Cardiovascular Outcomes” has been deleted.

Reviewer Hennesy

Reviewer: Three additional papers should be added:

   1. Added Schelleman et al. article (2012) and the Olfson et al. article (2012) to the systematic review. Results, table, and discussion were revised to reflect the addition of these two studies.
2. We chose to not include the Vitiello et al. study, because it did not have an appropriate endpoint. We specifically state in the review that endpoints such as blood pressure and heart rate are not included.

Other Revisions:

1. Moved section on mechanisms of amphetamines to introduction, and abbreviated it (page 4):

   Stimulants act by blocking reuptake of norepinephrine and dopamine as well as increasing their release into the extracellular space [12]. Stimulants may cause adverse cardiovascular events by 1) increasing blood pressure and heart rate [13-17], 2) inducing vasospasm through increased levels of circulating catecholamines [18-27], 3) causing vasculitis by inducing formation of circulating proinflammatory immunoactive glycation end products [19,28-31,31-38], and 4) prolonging the cardiac QT interval, which is associated with torsades de pointes [39-41].

2. Revised information on Qnexa to reflect that a FDA committee, during Feb 2012, recommended approval (page 5):

   In a reversal, an FDA advisory committee voted overwhelmingly to recommend approval of the drug, persuaded in part that the benefit of treating obesity outweighs the risk of adverse events [60].

3. We added emphasis on the importance of the problems of confounding and selection bias in this field (page 16):

   As the ability to control for confounding and selection bias increases, so does the confidence in the results of such studies.

4. We used the Olfson et al. article as example of confounding by contraindication (page 15):

   For example, in the study by Olfson et al., stimulant-treated patients with ADHD were compared to patients with ADHD not treated with stimulants. If the non-treated group was more likely to have contraindications to stimulant treatment, or had not tolerated prior stimulant medication trials due to adverse cardiovascular symptoms, then such confounding is a significant problem.

5. We deleted the paragraph in the discussion about Hennessy’s argument that propensity scoring should not be used. This was due to its lack of relevance, given that Hennessy himself used propensity scoring later, in his reviewed study (Schelleman et al., 2012).