Author's response to reviews

Title: Comparative safety of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: A systematic review and network meta-analysis

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Author's response to reviews: see over
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Dr. Sabina Alam
Editor-in-Chief
BMC Medicine

RE: MS: 2196165131514344

Dear Dr. Alam,

Thank you very much for considering our above-named manuscript. We are pleased that the *BMC Medicine* has invited us to submit a revised version of this paper.

We have carefully reviewed the comments made by the peer reviewers and have revised the manuscript accordingly. Enclosed you will find a point-by-point reply to the reviewer’s recommendations with line numbers referring to those found in the revised manuscript, which has been uploaded on your website. We look forward to receiving a final decision from your journal.

We have split our large systematic review into 2 papers, as recommended by the first reviewer. We will be submitting our second paper to your journal shortly and would like these to be published together, if possible.

Best wishes,

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Reviewer’s Comments and Responses: MS: 2196165131514344: Comparative safety of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: A systematic review and network meta-analysis

Our responses to the reviewers’ comments are outlined below in *italics* and have also been highlighted in the text using tracked changes.

**Reviewer 1: Anthony L Kovac**

(Major Revisions):

1. The paper is a complex analysis of a topic that has had a large number of publications in the last 10 to 20 years. The number of authors (20) is a large number for this type of analysis. It is a long paper to read and understand. I myself read it completely two times. The authors have done an excellent job, but I think the paper at 77 pages is TOO long and I think should be shortened. The material presented could probably be in 2 smaller papers, one of efficacy and one of safety. The title states that this is a "comparative safety" analysis. Thus, as such, I do not think that the authors have to include the efficacy analysis. This could be in another paper. Is it also absolutely necessary to have 29 appendices?

   Thank you for your suggestions. We have taken your advice and separated our original paper into 2 papers; one that focuses on safety and the other that focuses on efficacy. As such, the text has been cut in half for each paper, including the number of appendices. This was a large and comprehensive review, and as such a large number of reviewers were involved in the project. All 20 authors fulfill the ICJME authorship criteria.

2. Line 224: If a majority of the included experimental and quasi-experimental studies had unclear or high risk of bias or potential for funding bias, why did you include them?

   Please explain.

   In order to conduct our systematic review, we followed the guidance put forth by the Cochrane Collaboration (please see their Handbook at http://handbook.cochrane.org/). Specifically, this internationally renowned organization does not recommend excluding studies due to poor methodological quality. Instead, a sensitivity analysis is recommended to examine the impact of bias on the results and this is what we did in our paper. As you can see in our paper, the same results were identified when only studies with a low risk of bias were included in our analysis (see lines 254-257).

3. Lines 239-246: Is it really necessary to include the reference numbers for the 195 RCTs?

   *This is standard practice for systematic reviews, as outlined by the Cochrane Collaboration. However, we are happy to move the references to an appendix, upon request from the Editorial Board.*

4. Lines 260-267: Similarly, is it necessary to include the ref. numbers for the 175 RCTs?

   *This has been addressed in our response above.*
5. Lines 290-298: Similarly for the 238 RCTs. 
This has been addressed in our response above.

6. Lines 312-320: Similarly, Lines 353-359, Lines 368-373, etc. The text with all the references and the repetition is difficult to follow for this reviewer. 
Since we have shortened the papers, we hope that the references are not as confusing.

7. The paper appears to start related to the title on page 16 line 393. 
We have addressed this by removing the efficacy data and will present it in a separate manuscript

8. Lines 427-436: I am uncertain why was delirium included? This is a side effect of other anti-emetics, but not the %HT3 antagonists. 
The outcomes included in our paper were selected by health policy-makers, as well as clinicians. This was a safety concern for both groups of decision-makers so was included in our systematic review.

9. Discussion is hard to follow and should be simplified. 
The discussion section has been revised to reflect the safety results.

10. Lines 484-485: To this reviewer, the reason for doing this study should be stated earlier and included in the Introduction section. 
We added a sentence in the introduction section (lines 86 to 88) “We were commissioned by Health Canada, a department of the federal government, to determine the comparative safety of 5-HT3 receptor antagonists for patients of all ages undergoing surgery due to safety concerns regarding the 5-HT3 receptor antagonists.” and revised the second sentence in the methods to (lines 91 to 25) “The research users involved in this study who posed the original study question were from Health Canada.”

11. Lines 501-513: This should be in the Exclusion part of the Methods section and not discussion. 
This is already mentioned in our eligibility criteria (see lines 112 to 113): “Given the large number of included studies we limited the review to those published in English”
Since this is a limitation of our study, we also have to mention this as a limitation in our discussion section, as per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement (please see PMID: 19622551).

12. Lines 503-504: Why mention about chemotherapy studies. That is a totally different analysis and paper. 
As per the PRISMA Statement (PMID: 19622551), we need to report any deviations from our original protocol. Our protocol has been published and we originally intended to include chemotherapy studies. However, due to the extensive literature, we needed to split these topics into 2 separate papers. This is why we must discuss this in our discussion section.
Reviewer 2: Saurav Chatterjee

(Discretionary Revisions):

1. The network meta-analysis methods appear adequate. No further suggestions except that authors state that they only used Frequentist analysis, while its recommended to perform both frequentist and Bayesian with corresponding reporting of both including reporting of the prediction intervals.

Thank you for pointing this out. Although the presentation of both Bayesian and frequentist results would provide a thorough examination and a comprehensive study, this would make our manuscript unmanageable and very long.

The selection between Bayesian and frequentist approaches is an ongoing debate in the literature. In Bayesian framework, results can be very sensitive to the prior chosen for heterogeneity, and then the dilemma of selecting among the plethora of priors for heterogeneity arises. A related issue is also the choice between strictly positive priors or not. The use of non-informative priors, carrying no information about the true parameter value, is a common approach in the literature so that the results are data driven. In such a case, results of a Bayesian analysis approximate the results of a frequentist setting using maximum likelihood methods (see also Jansen et al ISPOR Value in Health 2014). But, even when vague priors are used, it has been shown (see Lambert et al Statistics in Medicine 2005) that results can materially change. The main advantage of the Bayesian approach is the inclusion of informative prior distributions on the model’s parameters. However, although Turner et al IJE 2012 provide the empirical distribution of heterogeneity, this is mainly provided for pairwise meta-analyses. Of course, the same problems exist in a frequentist approach and the selection of heterogeneity estimator. A recent review Veroniki et al. (In Press, Research Synthesis Methods) has shown that there are 16 different estimators available with varying properties.

A general recommendation is to use different heterogeneity estimators and compare the results, especially when only few studies are included in the meta-analysis – this is common in NMAs in which many pairwise comparisons often include only few studies. It has been also shown (see Veroniki et al International Journal of Epidemiology 2013) that the use of different heterogeneity estimators and assumptions (e.g., comparison-specific heterogeneity, common within-network heterogeneity, and common within-loop heterogeneity) might impact on the estimation of inconsistency, and this can importantly affect our decisions about NMA validity. Even the use of different inconsistency methods might conclude in differences in the results.

Including multiple methods for heterogeneity, inconsistency, in both Bayesian and frequentist settings would probably make a single paper unmanageable, as well as delaying dissemination of our findings to date. Moreover, according to the guidelines provided by The Cochrane Collaboration and the Comparing Multiple Interventions Methods Group, NMAs can be applied in either Bayesian or frequentist framework provided that all details about the assumptions and estimation methods are discussed in the text. And, in the reporting guidelines for NMA (PRISMA-NMA extension) that are in press, there is no requirement for inclusion of both
Bayesian and Frequentist analyses in NMA publications. We are involved with this latter publication.

We decided to use multivariate meta-analysis methods and apply network meta-analysis using mvmeta in Stata as suggested by White Stata Journal 2009 and White et al. Research Synthesis Methods 2012. We also selected the restricted maximum likelihood method to estimate the common within-network heterogeneity, as it has been suggested one of the best alternatives to the commonly used DerSimonian and Laird. Moreover, our networks include comparisons with only few studies, where estimation of heterogeneity is challenging. We assumed common within-network heterogeneity, so that comparisons including only few studies borrow strength from the remaining network.

2. Quality of written English: Needs some language corrections before being published. We have revised the paper and corrected the language, as necessary.