Author’s response to reviews

Title: Comparative effectiveness and safety of pharmacological and non-pharmacological interventions for insomnia: an overview of reviews

Authors:

Patricia Rios (RiosP@smh.ca)
Roberta Cardoso (CardosoR@smh.ca)
Deanna Morra (MorraD@smh.ca)
Vera Nincic (NincicV@smh.ca)
Zahra Goodarzi (Zahra.Goodarzi@albertahealthservices.ca)
Bechara Farah (BecharaF@cadth.ca)
Sharada Harricharan (SharadaH@cadth.ca)
Charles M. Morin (cmorin@psy.ulaval.ca)
Judith Leech (jleech@toh.ca)
Sharon E. Straus (StrausS@smh.ca)
Andrea C Tricco (TriccoA@smh.ca)

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Author’s response to reviews:

Reviewer’s Comments and Responses on Manuscript ID SYSR-D-19-00167 entitled "Comparative effectiveness and safety of pharmacological and non-pharmacological interventions for insomnia: an overview of reviews"

We have addressed the comments of the reviewers below in a point-by-point manner and our response is in italics. All changes to the manuscript have been documented using tracked changes, and the line numbers presented here correspond to those in the tracked changes document.

EDITOR:
Dear Dr Tricco,

Your manuscript "Comparative effectiveness and safety of pharmacological and non-pharmacological interventions for insomnia: an overview of reviews" (SYSR-D-19-00167) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am
pleased to inform you that it is potentially acceptable for publication in Systematic Reviews, once you have carried out some essential revisions suggested by our reviewers.

Review #1 has three main points: out of date search based on Systematic Review journal's guidelines, not assessing Risk of Bias using ROBIS [recommended by Chapter V in new edition of Cochrane Handbook], and not covering the time gaps from systematic reviews [also mentioned by Reviewer #2]. In addition, Review #2 mentions adding summary of finding table and I know that you already have one. It is good to have grading to the methods section as well and 'maybe' the reviewer means following new Cochrane Handbook so I attach the unpublished chapter of Cochrane Handbook on overviews just for the purpose of this overview and I request the authors not to share this chapter beyond this point as the chapter is not published. I also understand if this might be too much to do and the chapter was not available at the time you were conducting this overview so feel free to decline following the handbook and only reply the reviewer adding that you already have a summary of finding table.

The last comment form Reviewer #2 is about matrix of evidence and I know you have Appendix F. I suggest adding Matrix of evidence to methods section and referring to Appendix F tables in results however the reviewer also requests for covered area (CA) or corrected covered area (CCA) [doi: 10.1016/j.jclinepi.2013.11.007].

Response: Thank you for considering our work for publication, we have taken your feedback and the comments from reviewers under careful advisement and have undertaken as many of the revisions as we have resources to address. We recognize the importance of including the most up-to-date information possible in knowledge syntheses however we unfortunately do not currently have the resources to update the literature search for this overview as we have no further funding from the review commissioner to undertake one.

Furthermore, we appreciate your sharing the updated Cochrane guidelines for overviews of reviews but we do not feel they provide a substantial argument to support the additional completion of ROBIS along with the AMSTAR2 assessments we already conducted in our overview of reviews, which at the time it was conducted complied with Cochrane standards. Additionally, as stated above, we currently have no further funding to support this project and no resources to complete something like a ROBIS assessment for all of the included reviews in this overview.

We do, however, agree with you and Reviewer #2 regarding the utility of applying GRADE standards to our summary of finding table and calculating the corrected covered area (CCA). We have revised our summary of findings table (Table 3 in the manuscript) to include GRADE quality assessments of the evidence and have added the GRADE ratings to the results section (lines 252-261):

Out of the eleven classes of interventions included in this review, only two comparisons (melatonin compared to inactive controls and CBT compared to inactive controls) included reviews rated with a high strength of evidence based on GRADE and nine comparisons (benzodiazepines, non-benzodiazepines, suvorexant, anti-depressants, melatonin, CBT, behavioural interventions, and mindfulness-based interventions all compared to inactive controls; and CBT compared to active controls) included reviews rated with a medium strength of evidence (Table 3). Five comparisons included in this overview (anti-psychotics, diphenhydramine, and combination therapies all compared to inactive controls; non-benzodiazepines and anti-depressants compared to active controls) only included reviews rated as low or very low strength of evidence based on GRADE (Table 3).
discussion section (lines 388-391 and lines 400-402):
Additionally, the evidence for these interventions included reviews rated as having a high (melatonin) or medium (temazepam, triazolam, zolpidem, zopiclone, suvorexant, doxepin, and trazodone) strength of evidence based on GRADE.
The evidence for these interventions also included reviews rated as a high (CBT) or medium (CBT and behavioural therapy) strength of evidence based on GRADE.

and conclusion (lines 450-452):
“…can consider CBT as a first-line intervention due to its consistent evidence of effectiveness and a high strength of evidence across multiple outcomes…”.

Furthermore, we have developed an overall matrix of evidence for the overview (included as ‘Additional File 3) and have included the CCA in our results as follows (line 204-207):
A total of 358 index publications (primary studies) were cited 612 times across the 64 SR+MAs and SRs included in this overview; resulting in a CCA of 0.011, indicating little to no overlap across the included reviews.

Reviewer #1:
This is a well-designed overview with valuable summary with potential implications for practice. I found it easy to read and follow. I only have three major queries:
1: The search date is two years old (Jun 2017). As I remember, the search for the reviews should not be more than 14 months old at the time of submission (April 2019). Since this is important issue, I leave decision to the editor. Usually, the team explains this reason in cover letter to editor for example when the review has been submitted to an organisation (i.e. CADTH) within 14 months from search date, it may be acceptable if you mention this in the search methods.

Response: We appreciate your concerns over the timeliness of the material, the review was up to date at the time of submission to the commissioner (CADTH) and has since fallen out of date due to delays in attempting to get the manuscript published. Unfortunately, as the project was completed for the commissioner in the previous year, there is no longer funding available for our centre to undertake updating this overview.

2: The review team has properly used AMSTAR 2 for checking the methodological quality of included reviews however they have not assessed the risk of bias of the reviews using ROBIS. I think this component is necessary.

Response: We agree that ROBIS is an incredibly important tool for risk of bias assessments in an overview. However, at the time of our study conduct, the AMSTSAR2 tool was used widely and as such we feel that the application of AMSTAR2 in this overview is a sufficient assessment of the quality of the included reviews and complied with the Cochrane standards available at the time which indicate that quality of assessment of included reviews in an overview is sufficient.

3: The team used appropriate approach to prevent double-counting of studies. However, the search dates (time coverage) of included reviews have not been reported. Some of the reviews could be very out of date and require supplementary searches. If not possible, add in limitation please.
Response: Thank you for pointing that out, the lack of search dates was an oversight on our part and has been corrected. The literature search dates and coverage of the included reviews has been added to the summary of characteristics table (Table 1), detailed review characteristics (Appendix C) table, and the results section of the manuscript (lines 210-214):

Literature search dates for the included reviews ranged from 1996 to 2016 with more than half (62%) being conducted after 2010 (Table 1; Appendix C, Additional File 2). Only 11 (17%) of the included reviews searched databases from inception and a further 5 (7%) reviews ran searches going back more than 50 years.

Minor Comments
1: In eligibility criteria, geographical limitation of pharmacological interventions to Canada is unclear considering that such limitation does not apply to other types of interventions.

Response: The agency that commissioned the review is Canadian and they were interested only in interventions relevant to the Canadian marketplace. As such, we were obliged to limit eligibility of pharmacological interventions to those that are approved for sale in the country.

2: In Table 1, what does number 3 means in "Diphenhydramine (3)".

Response: Thank you for catching that, the inclusion of “(3)” after the drug name in Table 1 was a typo and it has been removed.

3: In Figure 1, 5024 minus 4480 equals 544 not 525.

Response: Thank you for finding that error! We have corrected the figure to more accurately reflect the number of records excluded after title/abstract screening – the number has been updated to 4,499 records instead of the incorrect number of 4,480.

I could not resist telling that your search methods are exemplary. Congratulations to your information specialists.

Response: Thank you! We are lucky to work with exceptional librarians!

Reviewer #2:
Nice overview of review following current recommendations of EBM groups.

Minor comment: 
1.- It would be grateful if authors can included a summary of findings table following GRADE approach for each outcome.

Response: We have revised Table 3 (Summary of findings) in our publication to reflect the GRADE approach as much as possible and have reported the GRADE ratings in the results section (lines 252-261):

Out of the eleven classes of interventions included in this review only two comparisons (melatonin compared to inactive controls and CBT compared to inactive controls) included reviews rated with a high strength of evidence based on GRADE and nine comparisons (benzodiazepines, non-benzodiazepines, suvorexant, anti-depressants, melatonin, CBT,
behavioural interventions, and mindfulness-based interventions all compared to inactive controls; and CBT compared to active controls) included reviews rated with a medium strength of evidence (Table 3). Five comparisons included in this overview (anti-psychotics, diphenhydramine, and combination therapies all compared to inactive controls; non-benzodiazepines and anti-depressants compared to active controls) only included reviews rated as low or very low strength of evidence based on GRADE (Table 3).

and discussion section (lines 388-391 and lines 400-402):

Additionally, the evidence for these interventions included reviews rated as having a high (melatonin) or medium (temazepam, triazolam, zolpidem, zopiclone, suvorexant, doxepin, and trazodone) strength of evidence based on GRADE.
The evidence for these interventions also included reviews rated as a high (CBT) or medium (CBT and behavioural therapy) strength of evidence based on GRADE.

and conclusion (lines 450-452):

“…can consider CBT as a first-line intervention due to its consistent evidence of effectiveness and a high strength of evidence across multiple outcomes…”.

2.- If possible, please provide a matrix of evidence using the covered area (CA) or corrected covered area (CCA) as figure.

Response: We have created a matrix of evidence for the entire overview (included in the submission as ‘Additional File 3’) alongside the individual matrices created for each intervention category and calculated the CCA for the overview. The overall matrix of evidence has been added to Appendix F as Table F12 and the CCA has been reported in the results section as follows (line 204-207):

A total of 358 index publications (primary studies) were cited 612 times across the 64 SR+MAs and SRs included in this overview; resulting in a CCA of 0.011, indicating little to no overlap across the included reviews.

3.- Include as limitation, lack of new RCT published not included in SRs, currency and coverage of SRs.

Response: Not reporting the literature search dates and coverages of the included reviews was an oversight on our part and has been corrected. The literature search dates and coverage of the included reviews has been added to the summary of characteristics table (Table 1), detailed review characteristics (Appendix C) table, and the results section of the manuscript (lines 210-214):

Literature search dates for the included reviews ranged from 1996 to 2016 with more than half (62%) being conducted after 2010 (Table 1; Appendix C, Additional File 2). Only 11 (17%) of the included reviews searched databases from inception and a further 5 (7%) reviews ran searches going back more than 50 years.