

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Melatonin for sleep disorders in children with neurodevelopmental disorders: protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials
AUTHORS	Jørgensen, Caroline Kamp; Hermann, Rikke; Juul, Sophie; Faltermeier, Pascal; Horowitz, Mark; Moncrieff, Joanna; Gluud, Christian; Jakobsen, Janus

VERSION 1 – REVIEW

REVIEWER	Ibtihal Abdelgadir Sidra Medical and Research Center, Doha , pediatrics
REVIEW RETURNED	29-Jun-2022

GENERAL COMMENTS	<p>Dear Authors,</p> <p>Thank you very much for submitting this manuscript for review. Very well constructed, Cochrane style systematic review protocol. Only few points to be considered for revision please:</p> <ol style="list-style-type: none">1. Abbreviation is to be introduced first time appearing in the text, the description of GRADE, TSA and DARIS is not easy to follow, so introduction of the concept first is recommended.2. The section of why is important to do this is not clear as by stating this review within the text indicates this current review. We can report it by e.g. (Author and colleague indicating name here) reported so and so..3. The inclusion of observation studies for assessment of adverse events is not recommended to be included in this review as it is only RCTs that were decided to be looked at, would suggest to remove it. If you decide to look at observational studies, separate methodology and a new protocol to be constructed.4. The assessment of heterogeneity included only subgroup analysis. This is only one section of assessment, I would suggest to discuss the other assessment tools – see Cochrane handbook of systematic reviews. <p>Kind regards,</p>
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REVIEWER	Elin Kimland Swedish Medical Products Agency
REVIEW RETURNED	21-Jul-2022

GENERAL COMMENTS	<p>Perhaps some issues to reflect on and mention in the introduction and later the discussion:</p> <ul style="list-style-type: none">- Melatonin can among included studies and original countries be used OTC, on a prescription and as a dietary supplement. This does not influence the suggested protocol or metaanalysis but can influence the basis of available randomised clinical trials.-Non pharmacological treatment is a common intervention often
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	<p>suggested before drug treatment and in combination with drugs treatment perhaps a clarification on how this will be regarded can be considered in the method section.</p> <p>-Why will only serious adverse drug reactions be included, perhaps this will be a limitation.</p> <p>-Valuable that you have highlighted the importance to perform similar analysis for observational studies to provide increased knowledge based on perhaps clinical experience.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Dear Authors,

Thank you very much for submitting this manuscript for review. Very well constructed, Cochrane style systematic review protocol. Only few points to be considered for revision please:

1. Abbreviation is to be introduced first time appearing in the text, the description of GRADE, TSA and DARIS is not easy to follow, so introduction of the concept first is recommended.

Author response: We thank the reviewer for this comment. We have now introduced the abbreviations where appropriate.

2. The section of why is important to do this is not clear as by stating this review within the text indicates this current review. We can report it by e.g. (Author and colleague indicating name here) reported so and so..

Author response: We thank the reviewer for this comment. We have now revised the text to clearly indicate which review is mentioned.

3. The inclusion of observation studies for assessment of adverse events is not recommended to be included in this review as it is only RCTs that were decided to be looked at, would suggest to remove it. If you decide to look at observational studies, separate methodology and a new protocol to be constructed.

Author response: We thank the reviewer for this comment. We will not search specifically for observational studies. However, if we identify observational studies that report adverse events associated with melatonin, we will report these narratively. This may ultimately warrant a systematic review of observational studies. As mentioned in the manuscript, these observational data will be reported in the supplemental material of the systematic review, and we will clearly state the limitations of observational data. We will not analyse randomised data with observational data, and the main results of the review will only be based on the randomised data. This has now been clarified in our revised manuscript.

4. The assessment of heterogeneity included only subgroup analysis. This is only one section of assessment, I would suggest to discuss the other assessment tools – see Cochrane handbook of systematic reviews.

Author response: We thank the reviewer for this comment. In the 'Assessment of heterogeneity' section, we describe how we will investigate heterogeneity. This includes χ^2 test, I^2 , and subgroup analyses as suggested by the Cochrane Handbook. This has now been clarified in our revised manuscript.

Reviewer 2:

Perhaps some issues to reflect on and mention in the introduction and later the discussion [NOTE FROM THE EDITORS: protocol manuscripts are not required to have a Discussion section, so there is no need to add one in response to this comment. Please attempt to address the reviewer comments as well as possible without adding additional sections]:

1. Melatonin can among included studies and original countries be used OTC, on a prescription and as a dietary supplement. This does not influence the suggested protocol or meta-analysis but can influence the basis of available randomised clinical trials.

Author response: We thank the peer reviewer for this comment. As stated in the protocol, we will include trials where participants in the experimental group are given melatonin at any dose, form (e.g. tablet, capsules, gummies, liquids), duration of administration, type of administration (e.g. oral), timing of administration, and setting. However, we plan to use subgroup analyses to assess whether the effects of melatonin differ per type of formulation. This has now been clarified in our revised manuscript.

2. Non pharmacological treatment is a common intervention often suggested before drug treatment and in combination with drug treatment perhaps clarification on how this will be regarded can be considered in the method section.

Author response: Thank you, we have now clarified how this will be addressed in the 'Types of interventions' section.

3. Why will only serious adverse drug reactions be included, perhaps this will be a limitation.

Author response: We will include both serious and non-serious adverse events as primary outcomes, i.e. all adverse events will be included in the analyses. This has now been clarified in our revised manuscript.

4. Valuable that you have highlighted the importance to perform similar analysis for observational studies to provide increased knowledge based on perhaps clinical experience.

Author response: We thank the peer reviewer for this positive comment.

VERSION 2 – REVIEW

REVIEWER	Ibtihal Abdelgadir Sidra Medical and Research Center, Doha , pediatrics
REVIEW RETURNED	01-Oct-2022

GENERAL COMMENTS	Dear authors, Thank you very much for this revised version, well written. The explanation of including some of the observation studies that comes through the search, while not probably searching for their inclusion is not recommended as will weaken the review and confusion can-not be taken from it. I recommend to either include observational studies following the recommended method of systematic review, or taking this part off from the results. kind regards,
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REVIEWER	Elin Kimland Swedish Medical Products Agency
REVIEW RETURNED	30-Sep-2022

GENERAL COMMENTS	I consider the changes in the revised manuscript to be in accordance with the comments received.
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VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

Dear authors,

Thank you very much for this revised version, well written.

The explanation of including some of the observation studies that comes through the search, while not probably searching for their inclusion is not recommended as will weaken the review and confusion can-not be taken from it. I recommend to either include observational studies following the recommended method of systematic review, or taking this part off from the results.

kind regards,

Author response:

We thank the reviewer for this comment. We agree that the current methodology may create confusion. We have therefore deleted the section regarding inclusion of observational studies. We will neither search for nor include observational studies in this review.