**Author’s response to reviews**

**Title:** Zolpidem reduces pain intensity postoperatively. A systematic review and meta-analysis of the effect of hypnotic medicines on post-operative pain intensity.

**Authors:**

Edel O'Hagan (e.ohagan@neura.edu.au)

Markus Hübscher (m.hubscher@neura.edu.au)

Christopher B Miller (chirs.miller@sydney.edu.au)

Christopher J Gordon (christopher.gordon@sydney.edu.au)

Sylvia Gustin (s.gustin@neura.edu.au)

Nancy Briggs (nancy.briggs@unsw.edu.au)

James H McAuley (j.mcauley@neura.edu.au)

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Systematic Reviews
Editorial Office

Dear Dr. Malic,

We are re-submitting a manuscript entitled "Zolpidem reduces pain intensity postoperatively: A systematic review and meta-analysis of the effect of hypnotic medications on postoperative pain" for your consideration.

Thank you for a very thorough and helpful review which we feel has improved the quality of our manuscript.

Please find our responses to specific queries below. Reviewer comments are in bold. Changes to the manuscript have been identified by page and line number.

Reviewer: 1- Comments to the authors:
1. Reviewer 1: Title: It might be useful to highlight the element of 'pain intensity' in the title. This is because there is another recent systematic review by Bjurstrom et al. that looks at this topic (although they are studying postoperative pain control and sleep promotion).
Zolpidem reduces pain intensity postoperatively. A systematic review and meta-analysis of the effect of hypnotic medications on postoperative pain intensity.

2. Reviewer 1: Introduction: Perhaps explore a bit more the bi-directional relationship between sleep and pain, particularly the implications ie. postoperative morbidity, and through this explanation introduce the concept of sedatives as pharmacological agents that could potentially reduce pain intensity. I am not sure if the sentence 'It is possible that pain intensity may be reduced by the administration of hypnotic medicines' and the bit on the 'low quality evidence that hypnotic medicines may have a role in postoperative pain management' (lines 27-28) have been deliberately repeated. I feel these should follow the explanation of the relationship between sleep and pain. I would also suggest being clear that the pain intensity being described in the sentence 'Pain intensity strongly predicts persistent postoperative pain' is 'immediate postoperative', as there are phases in postoperative recovery

Response:
We have rearranged the introduction in line with your comments. We have removed repeated sentences. We clarified that pain intensity immediate postoperative predicts persistent postoperative pain.

A consistent and strong predictor of persistent postoperative pain is intensity in the immediate postoperative period (6).

There is evidence that sleep quality and pain intensity have a bi-directional relationship (13). For example, sleep quality was found to be associated with next day pain intensity and daytime pain intensity was found to be associated with that night’s sleep quality for people with low back pain. These effects were independent of pain duration, depression and anxiety (13). Given this relationship, it is possible that hypnotic medicines administered postoperatively to improve sleep quality may lead to reduced pain intensity and persistent postoperative pain. This effect has never been systematically evaluated. To our knowledge this is the first systematic review to investigate the effect of hypnotic medicines on postoperative pain intensity.

It would be good to define the postoperative periods since this study appears to include all phases.

Response:
We have defined the postoperative periods.

Data were extracted for: immediate (up to 48-hours postoperatively), short-term (48-hours to 7 days postoperatively), medium-term (7-30 postoperatively), and long-term (greater than one month postoperatively) periods.
Not sure what is meant by 'duration of follow up'.
Response:
We deleted duration of follow up.

Change to the manuscript:
Pg 4. Line 26:
Deleted the duration of follow up

3. Reviewer 1: Methods:
Intervention-Perhaps indicate that all postoperative periods were included

Change to the manuscript:
Pg 6, Line 10:
The primary outcome was pain intensity, measured at any timepoint postoperatively.

4. Reviewer 1: Data items: It is good that extracted data items were included, but perhaps indicate the fields that relate to the topic of study i.e. drug being studied, measure of pain intensity etc.

Change to the manuscript:
Pg 7, Line 13-15:
Extracted data included information on trial design and funding, recruitment source, patient characteristics, intervention, control, outcome measure assessed, duration of follow up and results.

5. Reviewer 1: Appendix 2: Would it be possible to give a more thorough description of the secondary outcomes? I,e, how were sleep and other measured parameters assessed?

Change to the appendix:
Appendix 2, Line 8
2. Sleep quality or sleep efficiency

Appendix 2, Line 17-21
Sleep quality was measured on an 11-point sleep quality NRS, a 100 point VAS or the Richards Campbell sleep questionnaire. Disability was reported in 0 trials. Fatigue was reported in 3 trials (22) (24) (31), measured on an 11-point NRS or a 100 point VAS. General wellbeing was reported in 1 trial (31) measured on a 100 point VAS.

6. Reviewer 1: Results: Figure 4 is not very clear (dotted lines vs firm lines-what do these mean?)

Change to the figure:
Firm line indicates effect size
Dotted line indicates confidence intervals

Lor=lorazepam
Mel=melatonin
Mid=midazolam
Zol=zolpidem
7. Reviewer 1: Discussion: I am not sure it is fair to make this statement 'it is difficult to know the exact mechanisms of hypnotic medicines' without some kind of reference to back it up. Is there any literature that can explain/back up the opioid-sparing effects of sedative hypnotics? As both are CNS depressant drugs, would there be any proposed mechanism that leads to this, which may not necessarily be analgesic? Are there other factors in play?
Response:
We rewrote the discussion in line with your suggestions. We included a reference to support the opioid-sparing effects of sedative hypnotics.

Change to the manuscript
Pg 18, Line 14-15:
Deleted It is difficult to know the exact mechanisms of hypnotic medicines but

Pg 20, Line 5-11:
There is promising evidence for the usefulness of hypnotic medications as part of an opioid-free multimodal balanced anaesthesia strategy to achieve sedation necessary for major surgery (44). It is not known whether sedative hypnotics have an opioid sparing effect, though as both medicines are CNS depressant drugs, factors other than analgesia may be in play. These sedative effects of z-drugs should be investigated to maximise the parallels between achieving sedation and reducing pain intensity.

Were the paragraphs with the headings erroneously put under 'Strengths and Weaknesses'?
Response:
We corrected the paragraph headings.

Change to the manuscript
Pg 18, Line 11:
Deleted strengths and weakness of the study

Are there other areas of research that could be explored/carried out given the findings of this study? i.e. Does the type of surgery really matter? Are there any other factors that could have influenced these results?
Response:
We corrected the paragraph headings. We added suggestions for future research that could be explored given the findings, particularly in relation to the type of surgery.

Change to the manuscript
Pg 21, Line 11-14:
The trials we included that investigated the effect of zolpidem on pain intensity postoperatively were conducted on patients undergoing orthopaedic surgery. It is not clear whether the type of surgery or the patient population are important when investigating the effect of the hypnotic medications on pain intensity

Would it be possible to display how your findings relate to the current literature in this area?
Response:
We discussed our findings in relation to current literature.

Change to the manuscript
Pg 22, Line 2-3:
It supports evidence recent evidence that perioperative addition of melatonin or zolpidem may improve postoperative pain control (48).

Reviewer 2- Comments to the authors:
1. Reviewer 2: Page 4 line 3-4, please cite a reference to support this sentence
Response
We corrected this referencing in line with the recommendations from reviewer 1 to improve the introduction in point 2 above.

2. Reviewer 2: Page 10 line 3, "that" is written twice
Response:
Corrected

3. Reviewer 2: Fig. 2, the comparator is not placebo as written on the figure but analgesic medicines alone?
Response:
Corrected

4. Reviewer 2: It would be nice to see a figure for other comparisons: melatonin vs placebo, benzodiazepines vs other analgesics
Response:
We did not include a figure for other comparisons as there was only one study that compared the effect of melatonin vs placebo on pain intensity postoperatively and one trial that compared the effect of benzodiazepines vs other analgesics.

5. Reviewer 2: Secondary outcomes could be summarized in a table and integrated in the manuscript instead of as an appendix.
Response:
We made changes to the secondary outcomes in response to Reviewer 1’s comment number 5 above.
We summarized the secondary outcomes in a table and integrated it into the manuscript but also maintain the secondary outcomes as an appendix as we think that the reader would benefit from a full description of the outcomes.

Change to the manuscript:
Pg 11, Line 1-2:
Results for secondary outcomes are described in table 2 and reported in greater detail in appendix 2.

Kind regards,

James H McAuley
Full Author List
Edel O’Hagan, MSc; Markus Hübscher, PhD; Christopher B Miller, PhD; Christopher J Gordon, PhD; Sylvia Gustin, PhD; Nancy Briggs, PhD, James H McAuley, PhD.

Author Contributors:
I can confirm that all authors have read and approved the paper. All authors have contributed to the manuscript, each authors role is detailed below;
EO, MH, JMcA planned the study and developed the protocol. EO, MH, CM and CG screened titles and abstracts. EO, MH, CG, CM and SG completed the risk of bias assessments. EO extracted data which was checked by MH, CM, CG and SG. EO wrote the initial draft of the manuscript, and all authors critically reviewed successive drafts. NB provided statistical expertise. EO is the guarantor.

Corresponding author;
Name: Edel O'Hagan
Postal address: Neuroscience Research Australia (NeuRA), 139 Barker Street, Randwick, 2031, NSW, Australia.
Email address: e.ohagan@neura.edu.au. Telephone number: +61 (2) 9399 1618