Author's response to reviews

Title: Evidence for the use of Levomepromazine for symptom control in the palliative care setting: a systematic review.

Authors:

Isabel Dietz (Isabel.Dietz@helios-kliniken.de)
Andrea Schmitz (A.Schmitz@med.uni-duesseldorf.de)
Ingrid Lampey (lampey825@btinternet.com)
Christian Schulz (Christian.Schulz@med.uni-duesseldorf.de)

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Author's response to reviews: see over
Dear Prof Miriam Johnson,

Dear Ms Maria Merie Jul Ladag,

Thank you very much for this opportunity to send in a revised version of our manuscript after having received valuable reviewer feedback. We read the reviewers feedback en detail and we held two author team meetings to revise our manuscript in reaction to the different aspects that have been suggested.

Apart from a number of very helpful and valuable comments, which we addressed in detail (see table 1 and 2 below), we were also advised to improve the level of English in our submission. We would like to express our apology if this caused any inconvenience during the reviewing process. We have re-sent our final revised version to a native speaker and re-written a number of paragraphs to enhance the flow of the text. We hope that these steps have led to further quality improvement in using English as a foreign language.

The following paragraphs cover our detailed responses to the editorial comments:

1. Acknowledgements
After the Authors’ Contributions section can you please include an Acknowledgements section. Please also include the source(s) of funding for each author, and for the manuscript preparation.

We included the following paragraph on page 19: “We acknowledge Constanze Rémi from the Interdisciplinary Centre for Palliative Care in Munich, Germany, for her input from the pharmaceutical background. ID is founded by the Dr. Werner Jackstädt foundation, for the manuscript preparation no founding was obtained.” (page 19, line 6-10)

2. Tables
We note that you have uploaded the tables as figure files. Please remove them from the submission system and include the tables within the text file of the manuscript following the References section. Please also move the table title to above the table and the legend to below the table, within the text.

Done. (page 27-33)
3. Figure Legends
The figure legend and title should be part of the manuscript file, appearing after the Reference list. The figures are numbered automatically in the order in which they are uploaded by our online system.

Done. (page 34)

4. Footer
Can you please remove the footer from your manuscript file.

Done.

5. Additional Files
The Appendix, which has been uploaded as an additional file, should be cited as Additional file 1 within the manuscript text.

Done (page 7, line 20; page 11, line 24)

6. Line Numbers
Please include line numbers in your revised manuscript.

Done.

7. Copyedit
We recommend that you copyedit the paper to improve the style of written English.

As one of the authors of the present paper (IL) is native English speaker, we assume that a further copyediting process will not be necessary.

Responses to the referees' comments:

Referee #1:
I did think the text might not flow as smoothly as it could in some places.
Three examples:
1. In the concluding paragraph in the abstract, the authors correctly point out that evidence is limited before then stating that the drug has a number of beneficial effects. Arguably, no-one actually 'knows' if it works or not - people just 'believe' it to work. The following re-wording might make it flow more easily: "levomepromazine is widely used in palliative care for [list the indications]. However, the supporting evidence is limited to open series and case reports. Thus controlled trials are required to...."

The paragraph was changed to: "Conclusion: Levomepromazine is widely used in palliative care as antipsychotic, anxiolytic, antiemetic and sedative drug. However, the supporting evidence is limited to open series and case reports. Thus prospective randomized trials are needed to support evidence-based guidelines." (page 2, line 24-27)

2. In the final conclusion: "We emphasize, that we believe the amount of publications, which are at least mentioning levomepromazine, underlines, that there seems to be a clinical use and value for this drugs use in symptom treatment in palliative care patients and this deserves further evaluation". The following re-wording might again make it flow more easily: "Beneficial effects of levomepromazine are widely reported in the palliative care literature; it's role in symptom control therefore deserves further evaluation"

We agree and changed the sentence as recommended: "Beneficial effects of levomepromazine are widely reported in the palliative care literature; it's role in symptom control therefore deserves further evaluation." (page 16, line 23-24)
3. The authors already provide a helpful table of references giving an outline of the methods and findings of the papers. Expanding this a little might allow quite a lot of the text to be removed from the paragraphs. For example, the block of text describing the methods for, say, nausea, could be replaced by "beneficial effects of levomepromazine are described for nausea and vomiting in several open label series and reports (see table x); however this has not been confirmed in controlled trials", thus allowing the paper to be shorter and "punchier" without losing any of the content. This isn't an exhaustive list - there are a number of other places where the text might benefit from some re-ordering and re-structuring.

We have addressed this comment and re-wrote the whole manuscript to enhance the "punchiness" of the text. We hope that the outcome is convenient.

4. Consider clarifying "alfa1" (in the section on it's mode of action) as "alpha-1 adrenoceptor"

Done. (Page 4, line 5-6)

Referee #2:

1) Manuscript: Section “Methods”, paragraph “Data extraction and assessment of studies”, line 12: Level 5 instead of Level D

Right. Changed to level 5. (page 6, line 28)

2) Figures and Tables: Table 6: correct partial response to partial response

Changed. (page 32)

3) References: 52. Twycross R, ... line 3: incorrect citation style.

We are sorry, but we could not find an error. Please specify if this is still incorrect in the latest version.

4) Abstract section “Results”: starting line 1: “33 articles including ...” The addition of the numbers does not lead to 33 articles or the chosen formulation seems to be mistakable.

You are right, there were wrong numbers. Correct numbers are included and the sentence is changed as follows: “33 articles including 9 systematic reviews met the inclusion criteria: 15 on palliative sedation, 8 regarding nausea and three on delirium and restlessness, one on pain and six with other foci.” (page 2, line 17-19)

5) Manuscript section “Results”, paragraph “Study selection”: starting line 9: ‘27 out of these 33....’ The addition of the numbers does not lead to 33 or the chosen formulation seems to be mistakable.

This is true. We re-calculated and adapted the numbers and the sentence: “25 out of these 33 papers were found via automatic database searches and eight were found through reference tracking or hand searching.” (page 7, line 12-14)

6) Figures and Tables
a) Figure 1: Flowchart of study selection process: “Full copies retrieved and assessed for eligibility n = 84” is misleading compared to the numbers in section “Results”, paragraph “Study selection” line 7: “remaining 81 references full copies”
This was a typing error, number was corrected to 84 (as indicated in the flowchart) (page 7, line 9)

b) Figure 3: Table 2: PICOS approach in our systematic review according to the PRISMA guidelines: S = study designs: the type of study designs included in the review should be reported as shown in Section “Methods”, paragraph “Study characteristics” line 4: randomized controlled trials, prospective trials, cohort studies, case series, case reports, systematic reviews.

All right, table 2 was adapted. (page 27)

7) Appendix: Quality checklist STROBE with a total count of 32 points. I would like to recommend a short explanation why the authors use 32 items instead of 22 items for STROBE checklist.

We did use the original STROBE checklist with a total of 22 points, this is a typing errors that regrettably went through the whole document! We accordingly changed it in the appendix.

We hope that our efforts have been successful in convincing you to further proceed with the publication process. Thank you very much for your editorial assistance so far.

With the very best wishes from Dusseldorf, Germany, on behalf of the author team

Dr. Christian Schulz MD, MSc
Deputy Medical Chief