Author's response to reviews

Title: Opioids for chronic non-cancer pain: a protocol for a systematic review of randomized controlled trials

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Author's response to reviews: see over
To the Systematic Reviews Editorial Team:

We have received, and reviewed, the reviewers’ comments on our manuscript: *Opioids for chronic non-cancer pain: a protocol for a systematic review of randomized controlled trials*. We have addressed the reviewer’s comments in the order that they appear.

**Reviewer #1**

**1. Background: The background section is potentially a little too Canada centric in places.** (Discretionary Revision)

**Reply:** We have added the following information with respect to European data in an effort to expand our focus:

"*The National Center for Health Statistics estimates that 25% of the American population experiences CNCP [4] and Breivik et al. have reported a prevalence of 20% among the adult European population [5]."

And,

"*The cost of CNCP, taking into account direct medical expenses, costs of disability and lost productivity, is estimated at more than €200 billion per annum in Europe and $150 billion per annum in the USA [6] and is the primary cause of health care resource consumption and disability during adult working years [7]."
2. Limitations of Current Evidence: point 2: Use of “currently”. It is unclear whether this point is referring to the omission of studies only available at the time of the review or more recently published studies. (Minor Essential Revision)

Reply: We agree this is confusing, and we have removed the words "currently available" to convey that language restrictions in the prior review's search led to the omission of studies available at the time of the review:

"...the review only included trials published in English, Spanish or French, with the result that a number of eligible studies were not considered"

3. Limitations of Current Evidence: point 5: An important point is made about the use of the Jadad tool. However, the review could be viewed as being “of its time”, particularly as references supporting the point are all published after the review. (Discretionary Revision)

Reply: Agreed, and we have added the qualifier "subsequently" to convey this point:

"...the review used the Jadad scale to assess study quality [31], which has a number of limitations, including excessive consideration on reporting rather than performance, and which has been superseded by other superior instruments, including the Cochrane risk of bias instrument."

4. Methods – Eligibility Criteria: How will the range of chronic conditions (including remitting-relapsing symptoms) be defined for the purpose of selection. Terms for some of these are included in the search strategy – how/why were these decided upon. Are subgroup analyses planned around underlying conditions? (Minor Essential Revision)

Reply: Clinical experts on our team related that there are patients diagnosed with chronic pain conditions who have a remitting and relapsing pattern, such as migraine headaches, who are prescribed opioids in practice. We therefore felt that including remitting and relapsing conditions would improve the generalizability of our findings and provide more helpful information to both clinicians and patients.

For the purposes of our review we will include any condition that presents with chronic pain, not due to cancer, that has persisted for at least 3 months. The pain associated with such conditions can either be relatively constant or have a remitting and relapsing pattern:

"Eligible trials will include therapeutic trials that randomly allocate patients presenting with CNCP to an opioid analgesic or a non-opioid control. Chronic pain is defined as pain present for three or more months in duration, or as defined by the study authors as chronic. We will also include chronic conditions characterized by remitting and relapsing symptoms, such as migraine-related headaches."
We believe that most (if not all) chronic non-cancer pain (CNCP) conditions are associated with episodes of greater and lesser pain (e.g. chronic low back pain that ranges from 10/10 to 4/10 over time), but we agree that a subgroup analysis would be appropriate and have now added this analysis based on CNCP conditions that are associated with constant pain versus those conditions that are associated with episodes of pain interspaced with symptom-free episodes:

"We have generated the following a priori hypotheses to explain variability between studies: (1) functional syndromes (e.g. fibromyalgia) will show smaller effects vs. objectively diagnosed conditions (e.g. rheumatoid arthritis); (2) trials comparing opioids to placebo will show larger effects than trials using active comparators; (3) patients receiving disability benefits or involved in litigation will show smaller effects vs. those that are not; (4) weaker opioids will show a smaller treatment effect than stronger opioids; (5) CNCP conditions characterized by remitting and relapsing symptoms will show smaller effects than conditions associated with constant pain; and (6) trials with higher risk of bias will show larger effects than trials with lower risk of bias."

5. Methods – Meta-analysis: The sentence on baseline risk seems somewhat isolated and the point being made is unclear. Also how would the observational evidence be identified/selected? (Minor Essential Revision)

Reply: We have clarified that reporting baseline risk will be used to facilitate calculation of the absolute risk reduction, and that observational studies reporting baseline risk will be located through a search of the literature:

"We will also report the absolute risk reduction and acquire estimates of baseline risk from observational studies (located through focussed literature searches) or, if not available, from the median of the control group from eligible RCTs."

6. Methods – Meta-analysis – last sentence: It is unclear how the MIDs will be identified. (Minor Essential Revision)

Reply: We have included the following sentence to address this issue:

"We will conduct focused literature searches to identify anchor-based MIDs for relevant outcome measures."

7. Methods - Conversion to interpretable units (and beyond): There are two identical sub-headings related to conversion to interpretable units. The presentation of these headings, the sections of related text and their relationship to each other, figure 1 and other parts of the methods section requires considerable clarification. (Major Compulsory Revision)
Reply: We mislabeled the 1st sub-heading, and thank the reviewer for pointing this out. We have now relabeled the heading as follows:

"Conversion of WMDs to interpretable units"

We have removed the detailed example regarding conversion to interpretable units, and referenced Figure 1 at the end of the section about converting SMDs to interpretable units.

8. Methods - Conversion to interpretable units (and beyond): It is not clear how much of the information presented in both sections on conversion to interpretable units is related to or reproduced from the methodological papers (refs 38, 48, 49) by the same authors. Given the length of the article and the point immediately above also about this section, the authors should consider revising the text on these pages; where possible, referring to existing publications for deep detail of methods and retaining only the essence of such methods in the text to aid comprehension. (Minor Essential Revision)

Reply: We agree and have removed the detailed example regarding conversion of WMDs to interpretable units.

9. Methods – Addressing missing participant data: The implicit assumption(s) underpinning the application of missing data analysis to only significant treatment effects should be stated. Brief mention of how thresholds for important missing data will be determined would be helpful. (Minor Essential Revision)

Reply: Our revised manuscript makes, we hope, the process clear in the Methods section:

"We will use recently developed approaches to address missing participant data for dichotomous outcomes [51] and continuous outcomes [52]. When the primary analysis of our patient-important outcomes suggest important benefit, we will complete sensitivity meta-analyses to address missing participant data. For binary outcomes, if results are robust to a worst case scenario (all intervention group participants with missing data suffered the outcome of interest, all controls did not), we will conclude that missing data does not represent a risk of bias. If results are not robust to the typically implausible worst case, we will test progressively more extreme assumptions using methods proposed by Akl et al.[51] For continuous outcomes, we will use a parallel approach proposed by Ebrahim et al. using 4 progressively more stringent imputation strategies that are based on observed outcomes amongst those followed-up in the individual trials included in the meta-analysis.[52] Important changes in results with such sensitivity analyses will be interpreted to represent serious risk of bias."
10. Methods – Knowledge translation: Will patients/the public be involved in the research and the dissemination activities etc.? (Minor Essential Revision)

Reply: Our revised manuscript makes, we hope, the process clear in the Knowledge Translation section:

"The results of our proposed systematic review will be of interest to a broad audience, including patients diagnosed with CNCP, health professionals managing CNCP, employers, government healthcare benefits providers, insurers and compensation boards. We will involve relevant stakeholders from the onset of the review, in both research and dissemination activities, to improve the likelihood that the research results will be adopted and integrated into practice [56]."

11. Reference list: Several references are missing important information e.g. last accessed dates for web sources; identifying source (e.g.40) etc.. (Minor Essential Revision)

Reply: We have carefully reviewed our references for errors and omissions in order to address the reviewer's comments.

Attention by the reviewers has resulted in a number of improvements to our manuscript and we thank them for their efforts. We appreciate your attention to our study, and remain hopeful that our manuscript will be suitable for publication in Systematic Reviews. All authors of the original manuscript have read and approved the revised version of the paper.

We thank you for your time and look forward to hearing from you.

Sincerely,

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