Author’s response to reviews

Title: Perioperative use of gabapentinoids for the management of postoperative acute pain: protocol of a systematic review and meta-analysis

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Author’s response to reviews:

Thank you very much for all your comments, they were very much appreciated and the manuscript was modified accordingly.

Reviewer reports:
Please also correct the typo on p. 179 - should be "search" not "research" strategy

Reviewer #1: Perioperative use of gabapentinoids for the management of postoperative pain: protocol of a systematic review and meta-analysis

* Page5-Line 139: pooling some studies with resting scores and others with movement scores will potentially lead to heterogeneity. Regional analgesia is well known to decrease movement related pain compared to medications and it seems that you would not exclude them and treat them similar to other studies. Did you consider looking at them separately, OR do a sensitivity analyses with studies that report movement related pain scores?

- Thank you for your comment. We hypothesized that the context of pain assessment could potentially lead to heterogeneity. We plan to perform subgroup analyses based on the context of the pain
assessment (dynamic, rest or unknown) rather than separate analyses. We clarified this analysis in the methods section (line 239-240).

* Page 6-Line 150: I would suggest sticking to the term chronic postoperative pain. CRPS diagnostic criteria are not applied by most studies and this has led to inappropriate research conclusions.

-We thank the reviewer for this suggestion and agree with him/her. We will make the changes and consider looking at chronic pain as an overall outcome regardless if defined as such or as CRPS considering the well-known limitations you highlighted.

* Page 6-Line 160: You will include studies performing regional anesthesia and exclude studies with neuraxial analgesia with the reasoning that it requires different clinical expertise and resources.

  * What if a study includes shoulder or other orthopedic/trauma surgeries under single or continuous brachial plexus anesthesia, without GA? How is it different from neuraxial anesthesia in clinical expertise and resources?

-Thanks for your comment which highlights a lack of clarity in our protocol. We considered to include regional analgesia in addition to regional anesthesia (peripheral or neuraxial) when used as the main anesthesia regimen. We, however, exclude any type of regional anesthesia (peripheral or neuraxial) when used as a comparator. We modified our inclusion criteria accordingly.

* Page 6-Line 161: Please explain how do you expect initiation of gabapentinoids 1 week prior to surgery in patients having emergent surgery?

-We clarified this sentence. We meant that we will only include studies in which the intervention was started in the perioperative period (any moment in this time frame: one week prior to 12 hours after the surgery). We modified the sentence line 159-160.

* Also, how do you plan to deal with studies having patients with gabapentinoids administration for a chronic pain issue?

-Thanks for your comments - this is a very good point. We never meant to include these patients and clarified our eligibility criteria by adding this exclusion criteria.

* Selection Criteria: clarify your selection of studies published in non-English literature for final inclusion and analysis

-Thank you very much, we clarified this section.

* Page 8-Data Abstraction: Under this, you should also mention that you will extract data on risk of bias items

-Thanks. We also added this information in this section.

Statistical Analysis:

* Do you plan to conduct any sensitivity analyses?
We plan in conducting subgroup and sensitivity analyses as described in our methods. We modified this section to better reflect our analytical plan.

* As per above, you have nearly 11 or more subgroup hypotheses. It is suggested that conducting more than 6-8 subgroup hypotheses may not be methodologically appropriate. How do you support your approach?

-We are aware of the important number of subgroups planned but believe that these analyses are necessary to comprehensively understand the potential role of gabapentinoids. Considering an expected very high number of studies, such analyses are more acceptable from a methodological standpoint. However, we selected 6 subgroup analyses that will be performed for every outcome (line 242-245). All subgroup analyses will only be performed for our primary outcome measure. We are aware of the risk of type 1 error but believe that the benefit of our approach worth its limitation.

* Also, for each subgroup, it is expected that you indicate the potential direction of effect.

-We understand and appreciate the reviewer’s comments. However, unless considered mandatory by the editors, we would prefer not to lengthen this section. We believe the reader will understand the expected direction of these subgroup/sensitivity analyses and adding this information may only make this section heavier to read.

* Line 259-260[The fact that this drug is currently studied and used outside of * approved indication mandates its appropriate evaluation]-can be taken out as it does not add beyond the background provided in the introduction section.

-We removed this sentence.

* Page 12-Line 297: Funding: Should this not be better stated as "unfunded"? If the funds were used to support publication charges, it may be stated so to avoid any assumptions or potential funding bias.

-We modified this information – this study is not funded.

Reviewer #2: Verret et al: Perioperative use of gabapentinoids for the management of postoperative pain: protocol of a systematic review and meta-analysis

-Thank you for the possibility to read and comment on this protocol. The manuscript is well written with sufficient details and an easy to follow structure. I have some comments and suggestions and I will present them for each section:

Abstract: use of the term 'side effects' as a secondary outcome is somewhat misleading. You also use the term adverse effects in the methods section, under secondary outcomes. As there is a difference between side and adverse effects, I suggest that you stick to adverse effects (I recon the analgesic effect of gabapentinoids is a side effect of the anti-epileptic drug).

-Thanks for noticing. We modified “side effects” for “adverse events”.

Introduction: the word side effects is again used for the adverse effects of opioids and gabapentinoids - could you consider re-phrasing?
The introduction describes the core of the problem and states the importance and the urgency of this review.

-We agree that we should use “adverse events” instead of “side effects”. We modified accordingly in the whole manuscript.

Methods:
The choice of an aim that has a patient centred focus (with the patient centred primary outcome) should be commended. Though, it is not clear to me if the postoperative pain measurement will be both with patient reported tools and observational (clinical) tools? If you could specify this in both the primary and secondary outcomes, please? If you plan to mix the tools in the primary outcome, I would suggest an exclusively patient reported outcome to be very relevant as a secondary outcome.

-We thank the reviewer for his/her comment. We clarified our outcome measure of postoperative acute pain. The evaluation of postoperative acute pain will be made looking at the intensity of pain from the patient’s point of view - therefore, this outcome is clearly patient-centered. It is also the best available and most commonly used tool for pain assessment in clinical trials.

Inclusion/exclusion criteria: you could consider not to exclude studies based on outcome. There is also a great value of a systematic review, that contains all eligible trials on the subject, and where the problem with non-clinically relevant or non-patient-centered outcomes is addressed in a descriptive section of the results. Also, some authors may hold the outcomes of interest in a non-published form.

In order to ensure an exhaustive review and to draw appropriate conclusions on our outcome measures, from the primary to the secondary ones. We thus designed our eligibility criteria to include any trial looking at any of our outcome measures and not only for our primary one. We designed our study to adequately understand the potential role of the most important outcome measures that are patient-centered and/or clinically relevant.

Would you consider to exclude cross-over trials where both groups are treated with the intervention of interest (as a theoretically issue)?

-We understand the reviewer’s comments. We did not consider including cross-over trials considering that we are looking at acute pain within very short period after surgery. This short timing would not allow an appropriate washout period to adequately measure the effect of the intervention and the comparator. We clarified this in our eligibility criteria (line 162-164)

Search: how about conference proceedings (from the relevant conferences for the last 10/15 years?); ongoing trials found in clinical trial registries (hence, no restriction regarding publication status)?

-We thank the reviewer for his/her comment and agree that the search for conference proceedings is often useful in a search strategy when conducting knowledge synthesis work. In this specific review, we did not consider including trials from conference proceedings considering the very high number of trials expected and the fact that trials published in a conference proceeding format did not undergo a formal peer-review process. For these reasons, we are not convinced of the value-added for our specific research question and topic. We would thus prefer not doing so. We, however, added the search of the Clinical Trials.gov database for potential published trials that could have been missed.

Data extraction: I would suggest extracting the following study characteristics: year of publication,
countries participating, number of sites, total number of included patients, setting, types of patients, comparison drug (placebo, usual care, other drug).

-Thanks for your suggestion. We added the missing characteristics among those suggested in our data extraction form and in the manuscript. See lines 190-199.

I assume that you will prioritize data obtained from authors then data presented in other systematic reviews w meta-analysis (maybe the authors can confirm the correctness of this type of data) and lastly, extraction from diagrams or graphs using a web application.

-Thanks for your comments. We did not plan to include/extract data from other systematic reviews but only data published in the original publications. In case the data was not presented in a numerical format, but rather in a graph, we will extract the data using a web application designed for that purpose (WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/)). We clarified this in our manuscript.

Risk of bias assessment: will you judge the trials as overall low or overall high risk of bias, and do you plan to report a Risk of bias summary and Risk of bias graph? Will you perform your primary analysis only with the trials judged as overall low (if none are overall low, then a pre-defined cut-off for overall 'lower' risk of bias). This part of the methods section very important, especially as you state in the introduction, that you wish to use your systematic review to inform the recommendations. Hence, you should be very accurate on how you plan to judge and report the risk of bias in the included studies, and how you plan to support grading the quality and strength of your recommendations (when using the GRADE tool).

-We thank the reviewer for these comments. We realize that this section needed to be clarified in our methods. In order to assess the risk of bias of included trials, we will use the Cochrane risk of bias assessment tool which is designed to qualify (rather than quantify) the potential risk of bias of included trials between a low risk, a high or an unclear risk of bias. We will report the risk of bias of each trial in a figure along with our main work. Using the GRADE approach, we will also grade the quality of the evidence of our summary estimates. The potential risk of bias of the included studies is used to grade this evaluation downgrading the quality of the evidence when significant bias is observed.

Random errors: have you considered to include a sequential method (e.g. Trial Sequential Analysis) to account for random errors due to sparse data and repeated testing (in multiple meta-analyses)?

-We thank the reviewer for this important comment. Since the first iteration of this protocol submitted months ago, we added the performance of a trial sequential analysis to evaluate our primary outcome measure. This is now added in the revised version of the manuscript (lines 250-259). In addition, to facilitate the clinical interpretation of our primary outcome, we will then calculate the probability of observing an analgesic effect greater than the minimally important difference, defined as 10 points on a 100-point scale, following the OMERACT recommendations. This approach will allow us to calculate the proportion of patients achieving a clinically significant analgesic effect in each trial and also to pool results using the inverse variance method. We also added sensitivity analyses based on different thresholds of minimally important difference (20, 30 and 50). This approach is recommended by the OMERACT group [1].

Subgroup analysis: very good considerations regarding testing for sources of heterogeneity. I suggest adding a subgroup analysis of trials with overall low risk of bias versus overall high risk of bias to assess the effect of bias on the estimates.
Thank you for the comment. We already planned this subgroup analysis in our methods (line 313 and beyond).

I assume you only plan to perform Funnel plot if ten or more studies are included.

-Thanks for your comments - we added this clarification in the methods section.

With a few corrections and adjustments, this will become a SR w MA of great clinical importance, appropriate transparency and of very high quality.

Reference