Author’s response to reviews

Title: Adverse outcomes associated with opioid prescription for acute low back pain: A systematic review protocol

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Author’s response to reviews:

Response to reviewers’ comments

We have the pleasure in resubmitting a revised manuscript addressing the editorial and reviewers’ comments and we provide a point-by-point responses as outlined below. We would like to thank the editors for considering a revised and improved version of the manuscript and the reviewers’ for the helpful critique and valuable comments. Unrelated to the comments, we would like to point out that we have added Nitika Sanger as a co author based on her significant contribution to extensive revision of the manuscript and response to reviewers’ comments.
Editor comments:

1) Do you want to have a minimum duration of follow up for eligibility? I am just speculating, and perhaps you already know that the following concern does not exist. What if there are studies of very short duration, like 5 days or 3 days or even 1 day? I know in other treatments for acute low back pain there are 1 day studies, like an RCT of spinal manipulation compared to placebo with before-and-after measurements of pain. Since your concern is safety of opioids, is there a minimum duration of follow up that you want a study to have in order to consider it as evidence that safety was adequately assessed? Would 1 day of follow up be sufficient? Since you've chosen a 3-month dichotomy, would a 1 day or a 3 day study be pooled together with a study of 2 months duration?

Authors Response: Thank you for comment. We agree that there will be various durations of treatments of ALBP. However as we defined ALBP to be less than 3 months duration, we have chosen the 3 months as the cut off to identify adverse events occurring for the short term (<3 months) or long term (3 months or more). Our outcomes include opioid intoxication, withdrawal, Emergency Room visit and hospitalizations that can occur even with one day of treatment, while other outcomes including opioid use disorder and social adversity that may occur during a prolonged period of time. Therefore we will group any duration of treatment that is less than 3 months together. In the case of having many studies with only a small number of days of treatment, we will perform a subgroup analysis based on the days in treatment. Please see pages 11 lines 202-204 and page 14 line 276.

2) Your protocol specifies use of the D-L estimator for your random effects model. Did you consider use of the Hurting Knapp estimator? There was a recent critique of the use of the D-L estimator in situations that seem very likely to be present in this review, namely high heterogeneity/inconsistent effects.

Authors Response: Thank you for this comment. This point was also raised by reviewer 1 who suggested to remove this sentence which is now removed from manuscript.

Reviewer #1: I have reviewed this protocol with great interest. Given the absence of systematic review, this study will add relevant evidence for clinical practice. I really appreciate authors effort to develop this protocol. Nonetheless, there are major issues that need to be addressed before further steps.

1. Background_ line 52-53: Your major objective is about safety, not about effectiveness. Therefore this argument is not correct.
Author’s response: Thank you for your comment. We agree with the reviewer that the objective of the review is about the safety of opioids for ALBP and not the effectiveness. We have revised this statement in the manuscript. Please see on page 3 line 52-53.

2. Methods/design_ line 59: change clinical trials by Randomized control trials. In addition, Add information regarding how the quality of studies will be checked? How heterogeneity of studies will be checked? How publication bias will be checked? What model will you use to pool estimates?

Author’s response: Thank you for pointing this out. We agree this information is important to be included in the abstract and have made these changes to the manuscript. Please see page 3 line 59 and page 3 lines 62-65.

3. Discussion: Summarize what is known before in one sentence and add in this section.

Author’s response: Thank you for your comment. We have added this in the manuscript. Please see page 3 lines 66-67.

4. Systematic review registration: The title is different from the submitted manuscript “The risks of prescription opioid abuse following acute lower back pain: a systematic review and meta-analysis”. Check other inconsistencies as well.

Author’s response: Thank you for your comment. We apologize for this inconsistency and have made the appropriate changes on the PROSPOERO registration and have checked for other inconsistencies as well.


Author’s response: Thank you for pointing this out. We have reorganized and rephrased these sentences in the manuscript. Please see page 5 line 76-80.

6. Line 77: Acute pain or ALBP??

Author’s response: Thank you for pointing out this inconsistency. We do mean acute low back pain (ALBP).
7. Line 83 & 84: Which guidelines? I would prefer to name it.

Author’s response: Thank you for pointing this out. The guidelines are the guidelines of the American College of Physicians, American Pain Society and the European guidelines for the management of acute non-specific low back pain in primary care. We have added this in the manuscript. Please see page 5 lines 87-88.

8. Line 88: write numbers in words whenever it is below 100.

Author’s response: Thank you for pointing this out. We have made this change. Please see page 5 line 94.

9. Line 91: Be specific. Effectiveness, addiction, adverse events are broad topic. Introduce these topic in a very organized way if you are really concerned.

Author’s response: Thank you for your comment. We agree that these words are broad in the background. In order to avoid redundancy in the methods section we did not want to define each outcome in the introduction. Instead, to be more specific here and provide greater clarity, have changed the structure of this sentence to be a little more specific. Please see pages 5 and 6, lines 95-97.

10. Line 99: Is it different form opioids prescription? If so please define it. Otherwise, use it consistently either opioids prescription or prescription opioids.

Author’s response: Thank you for pointing this out. For this paper, there is no difference between opioid prescriptions and prescription opioids. We have made the changes in the entire manuscript to keep it consistent with prescription opioids. Please see page 6 line 105.

11. Line 108: Non-medical ??? Not clear. Is it over the counter drug or any non-physician prescriptions???

Author’s response: Non-medical opioid use is referring to individuals utilizing prescription opioids for illicit use which is outside of the treatment from a physician. This could include both over the counter (such as Tylenol number 1 which contains codeine that is in Canada is over the counter) or obtained illicitly. We have clarified this in the manuscript. Please see page 6 lines 114-116.

Author’s response: Thank you for your comment. We agree that these lines are not necessary and have removed them.

13. What is the difference between objective one and two? I believe obj 1 can be addressed by obj 2. Obj 3: Is it a kind of identifying susceptible groups?

Author’s response: Thank you for your comment. We agree that the first two objectives can be summarized within one sentence and have made these changes. Please see page 7 lines 129-132. Objective 3 is aiming to identify patients’ characteristics associated with adverse outcomes of opioid use which hopefully can help identify patients that may be susceptible to these adverse outcomes.

14. Line 129-137: Is it different from the above three aims???? If not, avoid repetition, merge together and summarize it. In general, the objectives are unclear.

Author’s response: Thank you for your comment. We agree that the previous section was redundant and have combined the two together and summarized as per your suggestion. Please see page 7 lines 123-134.

15. Methods and Materials. It is not well organized.

Author’s response: Thank you for your comment. We have used your suggestions for organization and added some of our own to help organize this section.

16. Add “Protocol and registration” subheading between line 138 & 139 and relevant explanations. See example from other published protocols.

Author’s response: Thank you for your comment. We have added this section with the information about the PROSPERO registration along with information about the reporting guidelines for the protocol. Please see page 7 line 136-139.

17. Line 139: Data source and Search strategy
Author’s response: Thank you for your comment. We have made changed this heading in the manuscript. Please see page 7 line 141.

18. Line 147-149: revise it.

Author’s response: Thank you for your comment. We have revised these lines. Please see page 8 lines 149-151.

19. Line 150-155: Focus on systematic ways of searching articles. Otherwise you will miss important studies. These three explanation are not systematic ways.

Author’s response: Thank you for your comment. In order to be inclusive and avoid missing important and relevant articles, we have included multiple ways of searches including a systematic review method as described in the manuscript and additional searches through reference lists of included articles, key journals and grey literature. Please see page 8 lines 143-157.


Author’s response: Thank you for your comment. We agree that this line is not necessary and have removed it.

21. Table 1:
   o This is not sufficient and difficult to replicate by other researchers.
   o Consult Medical Information specialist.
   o Develop a standard search strategy for all databases using relevant boolean operators. Look examples from previously published protocols.
   o Check whether generic or brand drug name used. It must be only generic name used as search word.
   • Supplement it as additional file.

Author’s response: Thank you for your comment and suggestions. We agree that only having one search strategy is not sufficient for this review. We provided one search strategy as an example for the purpose of this protocol. The study team is working closely with health Science Librarian
experienced in systematic search of literature (Laura Banfield). This search strategy for
MEDLINE has been approved by a Health Science Librarian as being inclusive. We are in the
process of approving this strategy and its corresponding operators with the librarian for the other
databases and will be providing the complete strategy for all engines in the final review paper.
We will be searching and providing a search strategy for Pubmed/Medline, EMBASE,
PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of
Science, the National Institutes for Health Clinical Trials Registry and the World Health
Organization International Clinical Trials Registry Platform (WHO ICTRP) in the final review.

22. Merge type of studies and participants section and use a subheading “Inclusion and
Exclusion criteria”. Organize either of the following ways:

- First inclusion then exclusion OR

- First studies inclusion and exclusion then participants inclusion and exclusion.

Author’s response: Thank you for your comment. We have used your suggestions for
organization. We have merged the two sections and first talk about the studies criteria and then
the participant criteria. Please see pages 9-10 lines 164-190.

23. Line 172-179: Will you exclude studies if any of these not reported?

Author’s response: Thank you for your comment. If the studies meet the requirements for type of
study and are investigating the use of prescription opioids, we will be including any study that
has reported at least one of the outcomes of interest, we will be including the study in the review.
We will only be excluding studies if they have not reported even one of the desired outcomes.

24. Line 186-187: such…delete this sentence.

Author’s response: Thank you for your comment. We agree that this sentence is not necessary
here and have removed it.

25. Line 195-198: In addition…..move it to statistical analysis section.

Author’s response: Thank you for your comment. We agree that this statement would be better
suited in the statistical analysis section and have moved it. Please see page 13 line. 242-245.
26. Line 204: Follow up duration six months...why?

Author’s response: Thank you for your comment. For our review, we want to look at both short and long term outcomes. We had to define short and long term outcomes in some manner because timelines of studies vary greatly in this population, and there is little in the literature to help define these lengths of outcomes in ALBP. We had to make a pre-specified definition of this ourselves. Therefore, we chose to define our short-term follow-up as less than six months and long-term follow up as six months or greater. We have added a brief explanation. Please see page 11 lines 202-204.

27. Line 208: delete this sentence “We will refer to the inclusion and exclusion criteria to assess study eligibility during screening.”

Author’s response: Thank you for your comment. We have removed this sentence.

28. Line 211: What Kappa value will you use as a cut-off point? If the agreement is low, what will you do?

Author’s response: Thank you for your comment. We will not be using a Kappa value cut-off, however we will report the value. If there is any disagreement between the 2 reviewers, we will resolve the disagreement by discussion and consensus. In the case of this disagreement can not be resolved, a third author will be consulted in keeping with systematic reviews methods.


Author’s response: Thank you for your comment. We have corrected the grammar and wording of this sentence so that it is clear. Please see page 11 lines 211-213.

30. Line 214-216: This is a result reporting format. Nothing related with selection of studies.

Author’s response: Thank you for your comment. We agree that this sentence is not necessary here and have moved it to the presenting of results section. Please see page 15 lines 299-300.

31. Line 218-226: Which one of them will be reported in the final result. Just focus only about these relevant information. Personally, for example the title of journal, is not relevant and other.
Author’s response: Thank you for your comment. We have modified this statement to only include the factors that we will be presenting in our final review. Please see page 12 lines 217-221.


Author’s response: Thank you for your comment. All the references will be managed through a Refworks account. We have clarified this in the manuscript. Please see page 12 lines 215-216.

33. Line 230: Newcastle-Ottawa Scale is recommended only for cohort and case-control studies. How will you check the quality of cross-sectional studies?

Author’s response: Thank you for your comment. We will be using a modified version of the NOS Scale that has been previously used in cross sectional studies (Bawor et al, 2014) to assess the quality and risk of bias in observational studies including cross-sectional studies. We have clarified this in the manuscript. Please see page 12 lines 226-227.


34. Line 244: Change statistical analysis by Data synthesis and Statistical analysis.

Author’s response: Thank you for your comment. We have made this change in the manuscript. Please see page 13 line 243.

35. Line 254-257: check duplication of idea. Remove first sentence

Author’s response: Thank you for your comment. We agree that this sentence is not necessary here and have removed it.

36. Line 261-263: If…. move it to subgroup analysis section.

Author’s response: Thank you for your comment. We agree that this statement would be better suited in the subgroup analysis section and have moved it. Please see page 14 line 276-279.
37. Line 268: We will contact study authors in order to verify key study characteristics…………
   Is it feasible?

Author’s response: Thank you for your comment. We have changed this statement to reflect that we will only be contacting authors if there is missing data that we need for the review. We understand that authors may not respond, moved, changed affiliations, etc. If there is no response, we will use multiple imputation strategies to deal with the missing data. Please see page 14 line 271-272.


Author’s response: Thank you for your comment. We agree that this statement would be better suited in the sensitivity analysis section and have moved it. Please see page 15 line 289-290.

Reviewer #2:

(1) Observational studies. The inclusion of observational studies is a critical feature of this review. An earlier systematic review found no RCTs comparing opioids with placebo for acute low back pain (Chou 2006), and a recent systematic review could only identify one related RCT (Shaheed 2016). Since observational studies might contribute to a considerable portion of your evidence, it deserves more detailed discussion. For example, you might need to design a more granular data extraction. It is recommended by Cochrane Handbook to place an emphasis on specific features of study design "rather than 'labels' for study designs (such as case-control versus cohort)". You might need to consider confounders or adjustment in your analysis as well, which is currently missing in the protocol. It is recommended by Cochrane Handbook that meta-analyses of non-randomized studies must consider how potential confounders are addressed. "Unlike for randomized trials, it will usually be appropriate to analyse adjusted, rather than unadjusted, effect estimates". If confounders or adjustment is considered irrelevant in your review, please provide brief explanation.

Authors Response: Thank you for your comment. We have elaborated on our inclusion criteria to include observational studies, specifically cohort studies with adjusted analyses. Please see page 10 lines 171-173. To summarize, two independent authors will judge the study design based on the methodology, rather than the label, and we will include cohort studies that examine the association between ALBP and our outcomes of interest. We will include all studies that adjust for age and sex as minimal potential confounders. We will not restrict eligibility based on other confounding variables as they will differ by outcome. Instead, we will capture the level of confounding bias for individual studies through quality assessment.
(2) Search strategy. In the Abstract, it states that "using a predefined search strategy". The word "predefined" is slightly concerning. Your search strategy should be agile to adjust for the sensitivity and precision of retrieved articles because literature searching is an iterative process. You could, however, have a "predefined" search filter. Examples include the Cochrane highly sensitive RCT filter and PubMed Clinical Queries. In your scenario, depending on how precise the result is, you might consider adding a filter for "adverse effects". Golder and Loke (2009) had a review on these filters.

Authors Response: Thank you for your comment. We agree that using a predefined search strategy is limiting. With the assistance of experienced health science librarian, we will pilot test a data strategy and see how sensitive it is and see if it works in terms of including relevant articles. Once a sensitive and inclusive search strategy is defined, we will standardize it and modify it to all the search engines. Since we haven’t not reached this step, the completed search strategy for all databases will be included in the final review. We have also removed the work “predefined” from the Abstract to avoid confusion. Please see page 3 line 55.

(3) Type of studies. It states that "no pilot or feasibility studies will be included in this review" as they are under-powered. I suggest you to examine the actual size of population (and power calculation) in the study, instead of looking for the keyword "pilot" or "feasibility". A pilot study could have a bigger population than a full-investigation yet small-scale study, let alone the possibility that a pilot study could have higher methodological quality than a full study. With that said, however, excluding small studies is controversial in general, as it defeats the purpose of summarizing totality of evidence, reduces the potential to explore heterogeneity and may miss information on important sub-groups (Grainge 2015). It is definitely fine for you to proceed with that decision, but it needs to be further explained.

Authors Response: Thank you for pointing this out. We agree that pilot studies may be well powered for the purpose of this review outcomes to be included in the analysis. While many may not have the desired outcomes, as they may just be looking at feasibility outcomes, we have removed this restriction to have a more inclusive search. Please see page 9 lines 166-167.

(4) Type of intervention. It seems that the current protocol only includes opioid as monotherapy, which is fine. However, it will be great if you could briefly discuss how to deal with co-intervention type of studies (exclude them?), such as a study on comparing naproxen with naproxen plus oxycodone.
Authors Response: Thank you for your comment. For our review, we will only be focusing on studies that have looked at opioid adverse outcomes. We will include studies that included co-intervention as long as they report on opioid related outcomes. Please see page 10 line 180-181.

(5) Type of participants. The exclusion of patients with comorbid substance use disorders is slightly concerning. If the prescriber determines that it is safe/necessary to order opioids for a patient in spite of his/her disorder, should this patient be included in the analysis to reflect the real world (adverse) effects of opioids? Is it possible to include these patients at the first hand, and subsequently perform sub-analysis without them to determine different (adverse) effects among otherwise healthy/unhealthy population?

Authors Response: Thank you for pointing this out. We agree that this cohort of patients is important and should be included. We have removed this as an exclusion criteria and will now perform sub-group analyses as per your suggestion. Please see page 10 lines 188-189.

(6) Type of outcomes. More details are needed as these outcomes are likely to be reported in various formats across studies. For example, how to handle "number of ER visits" versus "number of patients with ER visits", or how to handle all-cause mortality versus opioid-related mortality. On the other hand, social adversity as an outcome seems novel as it goes beyond the "classic" adverse effects of opioids such as sedation, confusion, nausea, constipation or respiratory depression. Nice job! You touch the rational of including these outcomes in Background and Discussion sections. If you could give a bit more details on the definitions of these outcomes in the Outcome section, it would be even better.

Authors Response: Thank you very much for your comments. We agree that including all these outcomes is extremely important. We have added more details about the outcomes. We agree that studies will have various definitions for their outcomes. We will be qualitatively summarizing them in the full review. Please see page 11 lines 197-200.

(7) Duration of outcome. Explanation is needed for the six-month cut point in grouping follow up duration.

Author’s response: please see response to reviewer 1, number 26
(8) Odds ratio. (This is optional) Please briefly explain why choose odds ratio over relatively risk for dichotomous data.

Author’s response: Thank you for your comment. There is no specific reason why we chose odds ratio over relative risk. We have just found that in this subject area, odds ratio is most commonly reported.

(9) Separate analysis. You could address this in Analysis section or Discussion section, but basically what would you do if the direction of (adverse) effects of randomized studies are different from non-randomized studies, or direction is the same but the size of effect is very different?

Author’s response: Thank you for your comment. We are going to be pooling the results of randomized and non-randomized studies separately. If the scenario is that the direction is different or the effect size if very different, we will conduct post-hoc subgroup analyses to determine if there are any confounding factors in the observational studies that is causing this effect. We will also address this is in the discussion and interpret how these results fit in with the current literature. We have added this in the statistical analysis section. Please see page 13 lines 263-267.

(10) Subgroup Analysis for substantial heterogeneity. Please elaborate on "opioid dose". If that means a cut point for high versus low dose, please justify the determination of that cut point. Or does that mean scheduled dosing versus as-needed dosing?

Author’s response: Thank you for your comment. We will be using the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain dosing recommendations as our cut-offs. We will have the low to moderate dosage cut-off at 90 mg morphine equivalents and below and the high dosage will be anything above 90 mg morphine equivalents. We have made this clarification in the manuscript. Please see page 14 lines 283-286.