Author’s response to reviews

Title: Treatment outcomes in patients with opioid use disorder initiated by prescription: A systematic review protocol

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Treatment outcomes in patients with opioid use disorder initiated by prescription: A systematic review protocol

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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 an improved version of the manuscript and the reviewers for the helpful critique and valuable comments.

Reviewer reports:

Reviewer #1: The proposed systematic review and meta-analysis addresses a critical and highly relevant research question during our current opioid crisis. As more individuals are becoming dependent on opioids through the use of prescription opioids, and the patient population of those requiring opioid substitution therapy is quickly changing, this review will be a useful resource for clinicians and researchers working to understand the shifting needs of opioid-dependent patients. Aside from a few minor issues and suggestions, this manuscript seems well-suited for publication in the journal.

Introduction/Rationale:

1. Page 4, line 96: ("illicit opioids use is associated with an increased risk of infection…").

--> This part of the statement seems quite broad, as infection could mean many things.

Authors Response: Thank you for your comment. This part of the statement has been modified to specify which types of infections are prevalent in the opioid use disorder population. Please see page 4, line 97.
2. The authors state on Page 5, line 124 that "variability in treatment outcomes may be partially explained by the way in which an individual is first introduced to opioids".

--> The paragraph that directly follows describes demographic shifts in the OST patient population as the underlying explanation for this variability. This paragraph alludes to inherent differences between OST patient populations who were first exposed to opioids via prescription vs. not, rather than the initial opioid itself. I don't think this is a problem, but it might require a bit of clarification (e.g., "variability in tx outcomes may be partially explained by a shifting OST patient population resulting from changes to the way in which an individual is first introduced to opioids").

Authors Response: Thank you for your comment. We have clarified the statement in this paragraph that helps to clarify that it is the differences in the way an individual is first introduced to opioids that is causing a shift in the OST population which may partly explain the variability in treatment outcomes. Please see page 5, lines 124-125.

3. Page 5, line 135-138: "Some studies show that this cohort of patients have better treatment response in comparison to people who obtained opioids illicitly [20], while other studies demonstrate that the introduction to opioids through a prescription increases the likelihood to misuse opioids and other illicit substances [21]."

-->As the first sentence in this paragraph (line 133-134) would indicate, these two statements are meant to demonstrate conflicting findings between studies with respect to OST treatment response among prescription and illicit opioids users, but they address two research questions that aren't directly comparable. The first statement describes OST treatment response between patients who began opioid use through a prescription to those who began opioid use through illicit opioids; the second statement describes initiation into opioid use via prescription opioids, but doesn't examine OST response. The second statement also alludes to a measure of risk for prescription opioid vs. illicit opioid, but the supporting study [21] is an exploratory qualitative study with descriptive statistics.

Authors Response: Thank you for your comment. We have changed the statement so that it is describing the treatment retention outcome for buprenorphine substitution therapy for prescription only users and heroin users. Please see page 5-6 lines 136-139.
4. How will the authors address patients who initiated opioid use through a prescription but are now using prescription and non-prescription opioids or non-prescription only?

Authors Response: Thank you for your comment. Our primary analysis will compare treatment outcomes for patients that initiated opioid use by prescription (and continue to use prescription opioids) to those patients that started using opioids through illicit means. If studies further report that the patients who initially began through prescription have transitioned to using non-prescription opioids (or both), we will conduct a sensitivity analysis by removing these studies to determine whether it has an effect on the outcomes. We have included this in the manuscript on page 14, line 267-272.

5. Will this review include individuals who began their opioid use via non-medical use of prescription opioids (e.g., obtaining prescription opioid from a friend or parent's prescription)?

Author’s Response: Thank you for your comment. We plan to include individuals who initiated opioid use through non-medical means (i.e. obtaining family or friend’s prescription) if the study compares these individuals to those who were introduced to opioids through a prescription for themselves. The individuals that began their use through a prescription not prescribed to them will be in the group of those that obtained opioids through other means (i.e. a family member, street or friend) as this can be defined as illicit use. This point is now clarified in the manuscript on page 7, line 178-183. We plan to conduct a subgroup analysis if possible examining the differences in treatment outcomes for individuals who obtained opioids through different sources (i.e. street, family members, friend). This point has been clarified on page 15 line 293-295.

6. The "outcomes and prioritization" section seems like it would fit better immediately following the "eligibility criteria" section.

Author’s Response: Thank you for your suggestion. The outcomes and prioritization section has now been moved after the eligibility criteria section. Please see page 8 line 193-200.
-Perhaps I am misunderstanding, but it seems that MEDLINE search line 19 should be "9 and 18" rather than "9 and 15" ("9 and 15" already appeared on line 16)

Author’s Response: Thank you for your comment. We have removed line 19 as it was a redundant line in the MEDLINE search strategy. Please see page 9, Table 1.

-Unless I am again misunderstanding, CINAHL search lines 13, 14, and 15 are off. Each of these lines contains that line. For example, line 13 says "12 AND 13", but if this were actually imputed into the search, it would yield a search error. It looks like line 10 has not been included in the final search, and I suspect the correct line 13 was supposed to be "10 AND 12", and was accidentally omitted, so line 14 was labeled 13, line 15 was labeled 14, and so on.

Author’s Response: Thank you for pointing this out. The lines were labelled incorrectly and this has been fixed. Please see page 11 Table 1.

Editors comments.

Thank you for submitting an interesting protocol on an important topic. I have a few minor comments:


Author’s Response: Thank you for pointing this out. This has been corrected. Please see page 2 line 66.

2. P8 Information Sources

Line 188. Clarify if both Medline and PubMed are to be searched, or which one of them. They contain slightly different data.

Author’s Response: Thank you for your suggestion. This has been clarified and it is Medline that is going to be searched. Please see page 8 line 205.
3. P14 line 270 Sentence does not make sense ‘signify an important among’ – please correct.

Author’s Response: Thank you for pointing this out. This line has now been corrected. Please see page 14 line 287.

4. Methods

The review states the authors expect to be able to determine if patients initially exposed to options through prescription differ in OST treatment outcomes compared to people who used opioids through illicit means. How do the authors plan to do this? Are there plans to compare the treatment outcomes identified in the review to treatment outcomes of people using opioids through illicit means?

Author’s response: Thank you for your comment. In this review, we plan to include studies that compare OST outcomes for patients who were introduced to opioids by prescription to those patients who were introduced by illicit sources. We will include comparative studies and conduct a meta-analysis to quantitatively summarize the effect of source of opioid introduction on OST outcomes. This review will be used to inform further primary research examining treatment outcomes by source of introduction in a current cohort of OST patients in Canada. This point is now clarified on page 7 line 166-168 and page 14 line 267-272.

5. Reference #15 is missing end of title and source details (Journal, volume, issue, pages, year….)

Authors response: Thank you for pointing this out. This has been corrected.

6. Mix of referencing styles used, some journal titles are in italics, some abbreviated journal names. Please check Systematic Reviews journal referencing style and apply to all references.
Authors response: Thank you for your comment. The references are now all in the same style and according to the journal referencing style.

7. Table 1. Medline line 19 is a redundant search line. The search should end at line 18 if the authors intend to remove animal studies.

Authors Response: Thank you for your comment. We agree that this is a redundant search line and have removed line 19 from the strategy. Please see page 9 Table 1.

8. Table 1. Cinahl search lines are incorrectly combined. Line 10 is a combining all ‘drugs’ searches so should be 1 OR 6 OR 7. Line 12 is wrong, these concept should be combined by AND rather than OR. However Line 13 can rectify this (and then you can remove line 12). Line 13 should read 10 AND 11. The result of that search line should be combined with line 9 using OR.

Authors Response: Thank you for your comment. We have made this change and added line 1 to line 10 so it reads 1 OR 6 OR 7. Please see page 11 Table 1. We have additionally consulted with our health science librarian and we believe that in the case of this systematic review, it may be important to keep line 12 combined with an OR because studies may not be categorized as both concepts or may not list those keywords in the title/abstract together. Some articles may not be indexed with Drug Prescription subject headings and you will need to use keywords to describe that to capture everything on the topic. In order to ensure we are able to capture everything, we think that keeping this line as OR may be best. We also combined search line 13 with line 9.