Reviewer’s report

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

Version: 0 Date: 31 Mar 2017

Reviewer: Junqiao Chen

Reviewer's report:

(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.

(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.

(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.
(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.

(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?

(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.

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

(8) Odds ratio. (This is optional) Please briefly explain why choose odds ratio over relatively risk for dichotomous data.

(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?

(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?

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