Reviewer’s report

Title: Serious adverse events reported in placebo randomised controlled trials of oral naltrexone: a systematic review and meta-analysis

Version: 1 Date: 27 Jul 2018

Reviewer: Stephanie O'Malley

Reviewer's report:

This meta-analysis examines serious adverse events in placebo controlled trials of oral naltrexone for a variety of conditions, excluding opioid dependence. This is an up-to-date analysis, that focuses on papers published since 2001 when guidelines for reporting adverse events in clinical trials were strengthened. This review yields important information supporting the safety of naltrexone compared to placebo as evaluated in over 10,000 patients. The paper would be improved by attending to the following issues:

Title: The title should be revised because studies of naltrexone for opioid addiction were excluded. Thus, the current title is inaccurate: "….trials of oral naltrexone taken for any condition…"

Line 37 - The listing of known side-effects should also cite the Croop paper (reference 31) and expand the list of known side effects to include some of the more common ones such as headache that were identified in that study.

Line 12 - What were the search terms that were used to search the electronic data bases?

Discussion: The discussion needs to remind the reader that the review excluded studies of patients with opioid addiction and was limited to studies of oral naltrexone. The conclusion should add the term "oral" prior to naltrexone.

Figure 3. The methods indicate that for studies with multiple naltrexone doses that results were examined separately, dividing up the number of participants on placebo for this comparison. However, in looking at Figure 1, it is unclear why only the 50mg dose from O'Malley 2006 is included when there were arms for 25mg and 100mg.

The reference list does not include references for all the included studies. This should accompany Supplemental Table 2 if not included in the main reference list.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

Acceptable

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I have been an advisory board member to Alkermes which makes a long acting injectable naltrexone. This paper deals with oral naltrexone.
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