Author’s response to reviews

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

Authors:

Monica Bolton (alan.mould@phonecoop.coop)
Alex Hodkinson (alexander.hodkinson@manchester.ac.uk)
Shivani Boda (shivani.boda@student.manchester.ac.uk)
Alan Mould (alan.mould@phonecoop.coop)
Maria Panagioti (maria.panagioti@manchester.ac.uk)
Sarah Rhodes (Sarah.A.Rhodes@manchester.ac.uk)
Lisa Riste (lisa.riste@manchester.ac.uk)
Harm Van Marwijk (H.VanMarwijk@bsms.ac.uk)

Version: 2 Date: 05 Sep 2018

Author’s response to reviews:

5th of September 2018

MS: BMED-D-18-00991R1

Dear Prof. Stephanie O’Malley and Dr. Panagiotis Zis,

Thank you for your email of 9th August 2018 which outlined the initial editorial decision that this manuscript is potentially suitable for publication in BMC Medicine, following our responses to the reviewers’ comments.

We are grateful for the opportunity to respond to the reviewer’s comments which have proven very useful in revising the manuscript. We have revised the manuscript and provided supporting
information where possible. We have offered a detailed summary of our responses to all the editor and reviewer comments and these are outlined in the document below.

We would of course be happy to provide further clarification about the changes if necessary and we look forward to hearing from you soon.

Kind regards,

Dr A. Hodkinson
Dr M. Bolton

NIHR School for Primary Care Research
Division of Population Health, Health Services Research & Primary Care
University of Manchester

Reviewer 1: Stephanie O'Malley

1. “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…”

We agree with this change and have now removed ‘taken for any condition’ from the title of the paper (P1: L2).

2. “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.
The Croop 1997 paper was not included in our meta-analysis because it was a non-randomised study. In response to the reviewers comment we have also expanded our discussion of possible side effects in the introduction (P5, L119-120): Known side-effects include nausea, vomiting, abdominal pain, decreased appetite, dizziness, lethargy, headaches and sleep disorders.

3. “Line 12 - What were the search terms that were used to search the electronic data bases?”

We have now included the full search terms in Appendix 1.

4. “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”.

We have added this to the discussion to remind readers that the review excludes opioid addiction participants and only involved studies of oral naltrexone post detoxification (P21, L498-499). ‘Oral’ has also been added to the conclusion preceding the naltrexone (P24, L572).

5. “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”.

We would like to thank the reviewer for this valuable point, which enabled us to clarify our methodological approach. A key requirement for meta-analysing adverse events in RCTs is that at least one adverse event is reported in one of the treatment arms (intervention or comparator group). Because there were no SAEs reported in the dosage groups 25mgs and 100mgs in either of the treatment arms in the O'Malley 2006 trial, meta-analysis was not possible. This is consistent with the Cochrane handbook guidelines for when handling double zero studies (i.e. studies which have zero events on both treatment arms) We have added a few sentences in the ‘Data synthesis and assessment of heterogeneity’ section which clarifies our approach (P13, L309-311): Studies with events in one arm only were included, by applying the continuity correction of adding 0.5 to all cells of a 2 x 2 table of results for each study (57,58) Double zero
studies (i.e. studies that report zero events in each treatment arm) were excluded from the analysis, as recommended in the Cochrane handbook.

6. “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”.

The full reference list of studies eligible for inclusion in this review are now in Appendix 2.

Reviewer 3: Panagiotis Zis

1. “The meta-analysis should also include the adverse event rate (not only the serious adverse event rate) in order to have a more complete picture of the genuine AE and the nocebo phenomena occurring during treatment with naltrexone.”

We would like to thank the reviewer for the overall positive remarks. Although the reviewer raises a reasonable query, the a priori focus of this meta-analysis was on serious adverse events for two reasons. The first reason is feasibility. SAEs were more consistently reported across trials and the data reporting allowed pooling using meta-analysis. There is solid evidence that reporting of AEs is inconsistent and incomplete across the studies to warrant pooling. For example, one of the largest studies in our review, Anton et al, 2006, only reported the top 5 AEs with no event rate for total AEs. Furthermore, in one of the largest reviews (Jonas 2014) which assessed naltrexone for alcohol use disorders, AEs were examined in 44 studies. Their key points highlighted that AEs were often not collected using standardized measures and the methods for systematically capturing AEs were often not reported. The type of reports also differed, for example, significantly different from placebo, more than 5% difference between groups, or specific AEs considered in that study. Finally, most of the AEs reported in their studies are of mild severity (nausea, dizziness, sleep disturbances etc.) (P22, L517-518).

The second reason is clinical significance. Since the publication of the Dalton review of duty of candour (2014), there is an increasing interest in understanding and preventing the occurrence of serious adverse events rather than any AEs because the former are more likely to lead to enduring or permanent patient harm. We now extensively discuss these issues in the ‘strengths and limitations’ section (P22, L518-521).
2. “The conclusion that SAE are not affected by dose, seem to be quite inaccurate as in the doses for 4.5 and 25mgs only one study on each dose was available”.

This is a fair point. We now clearly emphasise in the manuscript that these results should be interpreted with caution compared with the other groups (P19, L444-446). There were only two studies utilising lower doses of naltrexone, we have grouped them together into the dose group < 26 mg’s (figure 3).

3. “Apart from a statement that SAE rates did not differ between the different diseases, this is not clear and needs further clarification (i.e. tables/ figures). It has been shown that nocebo phenomena vary from disease to disease (i.e. there are lots of papers in neurological disorders) and therefore it is very important to be clear on this.”

Our assessment of the SAE rate by disease group is now shown in Appendix 5 via forest plot (P19, L446-447). This analysis did not display any statistical significance; however, we discuss some of the potential limitations of this analysis in the discussion (P21, L499-502). These results should only be considered as exploratory since classifying the populations into specific disease groups were quite difficult, and the results may have been hampered by nocebo (harmful) phenomena which, as reviewer 3 comments, have been seen to vary disease-by-disease in previous research (P22, L522-525).

4. “Age / Gender, year of publication and quality of RCT (i.e. risk of bias) should be included in the meta-analysis as these are confounding factors.”

We have taken this suggestion on board. We have performed univariate and multivariate meta-regression analysis to explore further causes of heterogeneity including covariates: age, gender, year of publication, length of trial and quality of study (i.e. low or ‘not all low’ risk of bias) (P13, L315-317). Our analysis which was exploratory did not reveal any significant outcomes (P18, L429-421). Furthermore, we include the forest plot for low vs. ‘not all low’ risk of bias studies in Appendix 6. Age, gender have also now been included in figures 2 and 3 alongside the study names.