Author’s response to reviews

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

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Author’s response to reviews:

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Dear Dr. Alessandro Recchioni,

Thank you for your email of 10th October 2018 which outlined the second editorial decision that this revised manuscript is potentially suitable for publication in BMC Medicine with the addition of further analysis following the responses to the reviewers’ comments.

The main concern raised by the reviewers was that an analysis of all AEs (in addition to SAEs which were our primary outcome) was not presented in the manuscript. In response, we have conducted secondary analyses on AEs. We found that less than one third of the included studies assessed AEs, and we discuss the implications and caveats of the AEs analyses.
We believe that these changes have significantly improved our manuscript but we are happy to provide further clarification if necessary. We look forward to hearing from you soon.

Kind regards,

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Reviewer 2 (Igho Onakpoya)

1. “That AEs are inconsistently reported is not a strong enough reason to exclude them from the review. Attempts could be made at getting more data from the corresponding authors, manufacturers, etc. Although nausea, sleep disturbance and dizziness are common adverse events does not necessarily indicate that they are all mild in intensity. Since the authors have already specified in their protocol that they were assessing SAEs, it would be helpful to explain upfront at the introduction why the review is focused on SAEs only.”

Response: Consistently with our protocol, the focus of our review on SAEs is more explicitly stated in the introduction. However since both reviewers considered the analysis of AEs important, we have added secondary analyses on AEs in the revised manuscript. We found that only 20 studies assessed AEs. Within a large list of 188 identified types of AEs, we only found 6 AEs (mild to moderate severity) which were more common in naltrexone groups compared to control groups. AE data are now fully described and analyzed in the revised manuscript (P18,
L419-422, appendix 6). As part of our review process we have contacted all authors. Our communication revealed no additional data on AEs.

2. “As a side note, the authors report that the studies were of high quality based on the GRADE criteria. However, I am unable to see the GRADE tables. It appears they have mixed up GRADE with ROB. If the authors did not formally conduct the GRADE-ing of the evidence, they should remove GRADE from the manuscript.”

Response: Thank you for drawing our attention to this omission. We now include the GRADE assessment results in addition to the Cochrane risk of bias results in the revised manuscript (P17, L405-408, appendix 5).

& Reviewer 3 (Panagiotis Zis)

1. “I still believe that for completion of the study a secondary meta-analysis of the adverse events should be carried out, even if only a proportion of papers report AE in detail.

Response: We have added secondary analyses on AEs in the revised manuscript. We found that 20 of the studies assessed AEs. Within a large list of 188 AEs, we only found 6 AEs (mild to moderate severity) which were more common in naltrexone groups compared to control groups. AE data are now fully analyzed and discussed in the revised manuscript (P18, L419-422, appendix 6).