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: 08 Aug 2018

Reviewer: Panagiotis Zis

Reviewer's report:

I read with great interest the paper by Panagioti et al. Meta-analyses of AE and SAE are important in the clinical setting and in clinical trial designing. Therefore, I think that this paper merits attention, however some revisions needs to be done before re-considering it or publication.

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.

2) The conclusion that SAE are not affected by dose, seem to be quite inaccurate as in the doses fo 4.5 and 25mgs only one study on each dose was available.

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.

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.

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.

Not applicable

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?
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I recommend additional statistical review

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Acceptable

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