Reviewer's report

Title: Factors associated with the prescribing of high-dose opioids in primary care: a systematic review and meta-analysis

Version: 0 Date: 12 Dec 2019

Reviewer: Katja Taxis

Reviewer's report:

This is a very timely paper, adding to the important discussion of opioid use. It is a very well written paper which is easy to follow. Methodologically it is well performed.

I have two main concerns:

The authors state correctly in the introduction "High doses of opioids are indicated in palliative care and cancer pain." The authors intended to focus on chronic pain treatment outside cancer. 6 of the 8 included study probably focus on patients with chronic pain. However, the two US based studies by Chang et al (2018 a and b) which include the majority of patients for this review, used IMS data (all-payer QuintilesIMS pharmacy claims). Few details on co-morbidities are available in the original studies. Description of the data sources suggest that they include a mix of patients, containing an unknown proportion of cancer or palliative care patients. This may become a major limitation of the systematic review. This should be discussed and the implications on the study findings considered. This should be reflected in rephrasing the conclusion as well.

A somewhat related point is that the majority of the studies also the largest studies have been performed in the US. There is only one European study, done in the UK. Therefore the results may be much less generalizable outside those countries. So more thought should be put into discussing the generalizability of the results, considering differences in prescribing policies and the health care systems in different countries, even if they are all high-income countries.

I have also a number of other suggestions:

- Abstract: Something incorrect with the I2 = 78.6.2% for male.
- Abstract: The conclusion is a shorter version of the main conclusion of the paper, but shortening it made it confusing and vague. Consider rephrasing to get a clearer message.
- Abstract: Add the number of studies in the abstract and the countries, i.e. the majority of data comes from US with the largest studies from there
- It would be enlightening from an educational point of view to include in the methods section some explanations in which cases you considered to calculate a NNT
- Some overview should be given which factors were tested in the different studies. It should be added in the results section which of those factors were not significant. If extensive, this could be put in a table in an appendix. If this was not a long list of factors, it may be also discussed as a limitation as so far, only a limited number of factors have been investigated.

- Put references behind the studies that are listed in the tables (the numbers, for easy to identify them from the list of references.)

- The percentage of patients on high doses vary very much across the studies this should be commented on in the discussion.

- Discussion: Tone down the repeated self congratulation with that this is the first study including starting the discussion with the term "to the best of our knowledge"

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**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.

No

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