Reviewer’s report

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

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Reviewer: Maria Panagioti

Reviewer's report:

This is a very well written systematic review and meta-analysis of the factors associated with prescribing of high-dose opioids in primary care. The main finding is that prescribing high-dose opioids in primary care is associated with concurrent prescribing of benzodiazepines, diagnosis of depression and A&E visits. These identified associations are likely to lead to avoidable patient harm.

Although a relatively small number of studies were included in this systematic review and meta-analysis, these were large observational studies based on millions of primary care patients. Overall, this manuscript would make an important addition to the current literature because:

* It is the first systematic review and meta-analysis on this topic, concerns a large proportion of the population and has major patient safety and cost implications
* The methodology is robust throughout including study identification, quality assessment, depth of analysis and statistical methods for analysis

Addressing the following points could strengthen the manuscript:

* It is surprising that prescribing of high-dose opioids is associated with co-prescribing benzodiazepines but not anxiety. Severity of anxiety and comorbidities might explain this finding which should be further discussed in the manuscript.
* It is unclear whether there is any existing guidance for the optimal prescribing dose of opioids in primary care or any interventions for optimising the prescription of opioids in primary care.
* As the authors point out there are varying definitions of high-dose opioids. Are there any alternative definitions for high-dose opioids and do the results differ using an alternative definition?
* The decision to focus on the primary care settings of high-income countries is reasonable but a limitation should be added in the discussion to state that the findings might not be applicable/generalizable in low and middle income countries.

**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?**
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

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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