Reviewer’s report

Title: Antipsychotic drug use and risk of stroke and myocardial infarction: a systematic review and meta-analysis

Version: 0 Date: 12 Sep 2018

Reviewer: Outi Mantere

Reviewer's report:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

This is a very comprehensive analysis with a strict and clear protocol and reliable analysis. However, even the methodologically best reviews are only as good as the original studies and here, the major limitation is that it was not possible to control for the type, dose and duration of medication and age at AP onset, among numerous other confounders. The interest seems to be decreased by the fact that the authors are not the first to review how AP associate with cardio- and cerebro-vascular disease. The search was done until May 2017. After all, I think they have reasonably identified a gap in the current knowledge. I hope my comments help in clarifying this point to the readers.

You should clarify in the introduction why you focus on these two outcome measures (instead of only one or several). The readers should see the novelty of the findings. It is true that you convincingly describe the quality of your work as compared to the others, but you could improve description of how people should change their behavior based on the results as compared to previous knowledge (or lack of knowledge).

To my understanding, you exclude existing register studies; this should be recognised with a discussion of reasons and consequences. The findings from the register studies could still strengthen your findings and often have better knowledge about the time aspects.

Common indications for AP use include also symptoms such as behavioral problems, sleep problems or anxiety. Do you think you covered these indications and reports and how did this affect the possibility to generalize the findings?

A clinically important and interesting part of your discussion is the effect in acute vs chronic phase of the illness. Do you think that an interaction between the age at AP onset with duration of medication is likely for MI or stroke or both? Would you data provide any further insight to whether analysis of additional predictors (blood values, family history) should be identified in a specified age group at onset of AP treatment?
Although partly discussed already, you could possibly add some more detail about what an optimal future study would look like to respond to the most significant open questions (symptom profile, age, time in follow-up). Since you had different settings in the original studies, you could possibly comment also the feasibility vs advantages of case-control vs register studies, family studies, naturalistic vs RCT etc.

Some studies support that even early phases of severe mental illness present symptoms of a vascular disease (see e.g. Benjamin Goldstein in early onset BD), before metabolic side effects.

Please check "There was no clear evidence of an associated between AP drug use and risk of MI. However, substantial statistical and methodological heterogeneity between among a relatively small number of studies on MI risk makes it difficult to draw firm conclusions".

**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.

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
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal