Author’s response to reviews

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

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Technical Comments:
1. PRISMA Guidelines - In accordance with BioMed Central editorial policies (http://www.biomedcentral.com/submissions/editorial-policies#standards+of+reporting), could you please ensure your manuscript reporting adheres to PRISMA guidelines (http://www.prisma-statement.org/) for reporting systematic reviews. This is so your methodology can be fully evaluated and utilised. Can you please include a completed PRISMA checklist as an additional file when submitting your revised manuscript.

Please complete the checklist in full by inserting the page number/paragraph and section of your manuscript which reports the information that meets the criteria of the checklist. For example, “Methods, paragraph 2”. If a criterion is not applicable for your particular manuscript/study, we can accept “N/A”.

Authors’ response: We have added the PRISMA checklist to our submission documents

Please note that checklists completed incorrectly will be returned for revision as we cannot progress your manuscript to peer review until the checklist has been completed.

2. Title Page - Please include the email addresses for all authors on the title page. The corresponding author should still be indicated. Please also ensure these email addresses match the email addresses provided in the editorial manager system.

Authors’ response: We have added all email addresses to the title page
3. Please change introduction section heading to background in the manuscript body.
Authors’ response: We have made this edit

Reviewer 1 comments:

Outi Mantere, M.D., Ph.D. (Reviewer 1): 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.

1. You should clarify in the introduction why you focus on these two outcome measures (instead of only one or several).

Authors’ response: Major mental illness is associated with an increased cardiovascular disease incidence and mortality, which is largely due to ischaemic heart disease and stroke. We have clarified that in this review our focus is therefore on major cardio- and cerebro-vascular events – i.e. stroke and myocardial infarction. We have edited the introduction section to make this clearer (Page 4, paragraph 1, line 5; page 4, paragraph 2, lines 3-4; and page 6, paragraph 1, line 14).

2. 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).

Authors’ response:
Thank you for this comment. In the absence of conclusive evidence on the association between AP use and major CVD events in different sub-populations, we exert caution when recommending behaviour change. However we do urge caution in the use of off-label AP drug use and the need for monitoring of CV risk factors prior to and during treatment. We have included this on page 17, paragraph 2, lines 1-5: “In the absence of conclusive evidence that AP drug use increases risk of stroke or MI, we recommend that clinicians should carefully weigh the potential benefits and risks of AP drug use on an individual basis, and evaluate cardiovascular risk prior to AP drug initiation and during treatment. We urge clinical caution in the initiation of off-label AP drug use and encourage the exploration of alternative treatment routes.”

3. 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.
Authors’ response: Thank you for this comment. It would be helpful if you could clarify what you mean by ‘existing register studies’. Our review focused on published articles, with no restriction on type of studies. Articles could include general populations (e.g. be based on prescription medication datasets linked to other datasets to identify CVD outcomes) or specifically people with major mental disorders.

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?
Authors’ response:
Overall, our ability to generalize the findings was limited to the antipsychotic indications reported in the studies. Studies usually specified schizophrenia, bipolar disorder or dementia/behavioural and psychological symptoms, however many studies also reported on a ‘general’ antipsychotic use group, which presumably includes all of the above indications and anxiety, sleep problems etc. Therefore, it was difficult to generalize findings to a specific indication of antipsychotic use.

4. 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?
Authors’ response:
Thank you for this thoughtful comment. Unfortunately, since our review is limited by what is reported in primary studies, we could not explore whether other factors such as blood values or family history should be identified in particular age groups at onset of AP treatment. The suggestion that the risk of stroke/MI is greater in the acute versus chronic stages of treatment is indeed interesting. This evidence stems largely from the self-controlled case series/case-crossover type of studies, which usually included an older general population and so may not have included many people with a psychiatric disorder for which AP drugs are usually prescribed. Therefore, we cannot really comment on there being a possible interaction between age at AP onset and duration of medication. Rather, we can only say that it seems that, possibly irrespective of illness phase, the acute phase post-initiation of AP drug use may represent the phase in which stroke and MI risk might be greatest. We have expanded our discussion of this on page 14, paragraph 1, lines 14-23.

5. 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.
Authors’ response:
We have added more detail about what future studies should look like on page 16 (2nd paragraph, line 1) to page 17 (1st paragraph), which now reads:
“Further research is needed to address the gaps identified in this review. For ethical reasons, RCTs in this area are less feasible than observational studies, since, for some conditions, there are no suitable potential alternatives to antipsychotic drug treatment. However, where potential alternative treatments do exist, RCTs may be appropriate. In the dementia population for example, future studies could examine how the risk of stroke and MI amongst AP drug users compares to alternative treatment for
behavioural and psychotic symptoms. For example, findings from a cohort study conducted by Finkel may suggest that AP drug use has a potentially lower risk of stroke compared to the use of benzodiazepines in dementia patients [69]. Where RCTs are not feasible, robust cohort and case-control studies should be performed. Such studies should be sufficiently large in order to be adequately powered to detect significant associations with high precision. Pooling of individual patient data across multiple settings would be one approach to enhance study power. Routinely collected national health data which contains information on mental health diagnosis and treatment, previous and subsequent cardiovascular events and confounding factors would be the ideal data source for future studies. This relies on the existence of robust mental health registries linked to other health data or linkage of primary and secondary care data as well as prescription data, which exists in relatively few settings. However, such studies would eliminate bias, facilitate control of confounders and establish temporality between AP drug use and cardiovascular outcome, particularly in case-control studies. Future studies should also distinguish between FGA and SGA users, given their differing pharmacological properties and potentially different risk of stroke and MI. Confounding by indication should be minimized and risk estimates should be determined based on indication for AP drug use. Studies should also assess the risk over multiple time periods in order to clarify whether and how the association may change with time. A minimum duration of AP use should also be clearly established (such as multiple prescriptions) especially if large registry databases are used to ascertain exposure.”

6. 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.

Authors’ response: Thank you – indeed, this is an important point and relates to our criticism of the lack of control for confounding by indication in many of the studies identified in our review. We have expanded our discussion of this to highlight the complexity of the association between psychiatric illness and excess cardiometabolic risk (page 15, paragraph 3, lines 5-7 to page 16, paragraph 1, lines 1-4):

“ The excess risk of cardiovascular disease in people with major mental illness is thought to be multifactorial and to include poor lifestyle behaviours (such as smoking, alcohol misuse, physical inactivity and obesity), increased risk of diabetes, shared genetic factors and direct physiological effects of the mental illness [65–67]. Whilst APs might themselves increase the risk of cardiovascular disease, particularly through weight gain, it is interesting that metabolic dysregulation for example, has been observed in AP naïve people with major mental illness [68].”

7. 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".

Authors’ response: We have corrected the typo, changing ‘associated’ to ‘association’.

Reviewer 2 comments
This is a systematic review and meta-analysis to evaluate whether use of antipsychotics is associated with increased risk of stroke and myocardial infarction. The search was based on major electronic databases from database inception through May 28, 2017 and concerned observational studies. Ten studies on MI and 19 studies on stroke were considered eligible. Significant increase in risk of stroke was associated with second generation antipsychotics (SGAs) among cohort studies [pooled HR 1.71, 95% CI 1.16 to 2.53; Figure 2b]. Use of any antipsychotics in patients was not associated with MI risk. The authors conclude that the available evidence suggests that the use of any antipsychotics significantly increased the risk of stroke, but risk of MI remains unclear.
Comments
1. This paper/study confused drug categories between antidepressant and antipsychotics. They authors used confounders in confounding adjustment from the included studies as drug exposure and received incorrect the estimate in their meta-analysis. The conclusion therefore was misleading.

Chen (2008) and Correll (2015) indeed investigated antidepressants use and risk of cerebrovascular accidents (CVA). The authors misunderstood the concept of confounding adjustment. They used confounding effects on the risk of CVEs from the use of other medications that are known or proposed to affect risk of CVEs such as risperidone as SGA use vs no use in their meta-analysis. In fact, Chen’s Table2 was Hazard Ratios for the Risk of CVEs Associated with the Use of Antidepressants. Correll’s study used SGA use and antidepressant use as covariate in the model, which cannot use in this study. The similar mistake was found when the meta-anlaysis included Lan et al, 2015 (stroke with lithium exposure in bipolar disorder). The results and conclusions, therefore, are misleading.

Authors’ response: We have carefully reviewed these articles. We can understand why the reviewer has questioned whether we have included the correct data from Chen, but we believe that Table 2 in Chen is simply poorly labelled, which has created confusion for the reviewer here. Whilst the title of Table 1 is “Hazard Ratios for the Risk of CVEs Associated with the Use of Antidepressants”, the authors have included effect estimates for the association between antidepressants (both adjusted and unadjusted) and CVEs, and also other factors, including risperidone, and CVE risk. We draw the reviewer’s attention to the results section of Chen et al (page 180, second paragraph), which clearly states the adjusted HRs for the effect of antidepressants on CVE risk and the statement: “Use of aspirin, anticoagulants, risperidone, or amphetamine; comorbid substance abuse; and a history of diabetes, hypertension, cardiac diseases, or hypercholesterolemia may be associated with an increased risk of a CVE.” The latter refers to the HRs for the associations between each of these non-antidepressant factors and CVE risk, as presented in Table 2. We do not believe that there are any errors in our understanding of adjustment for confounding and are confident that we have extracted the correct data from this article.

Correll et al compared outcome events, including stroke, among SGA users versus people taking antidepressants, but not SGA drugs. The authors of this article justified their comparison group of people taking anti-depressants but not SGA drugs in terms of balancing potential confounders related to mental illness and SGA initiation (i.e. they attempted to control for confounding by indication). We believe that this is a sensible approach and given the lack of control for confounding by indication in most studies, did not think that it would be sensible to exclude this study from the review. We have amended our methods section to more accurately reflect our inclusion criteria (page 6, paragraph 2, lines 7-10) and have added explicit details about this study to the result section (page 8, paragraph 3, lines 16-18). We have similarly reviewed the article by Lan et al. In this study, the authors presented data on the association between lithium use and stroke risk in a cohort of bipolar patients using two approaches, one of which included an unmatched cohort of people with bipolar disorder. In this unmatched cohort, they examined the effect of lithium use on stroke risk, but they also examined the effect of other exposures on stroke risk, including AP use (as presented in table 2 of their article, which shows mutually adjusted HRs for each factor). This is where we extracted data on AP drug use and stroke risk. We also direct the reviewer to the description of these results in the paper (page 708, column 2, first paragraph: “Neither typical (HR = 0.95, p = 0.6784) nor atypical (HR = 1.05, p = 0.6992) antipsychotic agent use was significantly associated with the risk of stroke”.

2. The authors did not explain the reasons why Douglas et al., 2008 was included in Table 1, but eventually was excluded in meta-analysis.
Authors’ response:
We did not include results from self-controlled case series, case-crossover studies or case-case-time control studies because it would not have been methodologically sensible or appropriate to pool these with cohort or case-control studies (given differences in study design and analytical approach). We have clarified this by adding the following sentence to the methods section (page 7, paragraph 1, lines 2-4): “Whilst we summarized findings from self-controlled case series and case-crossover studies, we did not include these studies in our meta-analyses, given the differences in study design and analytical approach.”
Rather than including these studies in a meta-analysis, we summarized their findings in detail on page 10, paragraph 2, which we draw the reviewer’s attention to.

3. The authors kept mentioning and quoting ‘general’ population. I don’t see any necessity for it. It is unnecessary to use ‘general’ population (e.g. a cohort identified from primary care/medical insurance records) again.

Authors’ response: We have defined what we mean by general population on page 6, paragraph 2, lines 1-2) and have removed the quotation marks thereafter.

SIGN 50 checklist was used as the tool of quality assessment. Although SIGN checklist may be developed for the critical appraisal of observational studies, SIGN 50 checklist is used mainly for guideline development. For observational studies, here Newcastle-Ottawa scale (NOS) is more appropriate. Besides, NOS evaluates whether exposed and non-exposed cohort represent the general population or the average in the community. Using NOS, the study does not need to make any redundant quote of “general population.” Not using a tool of quality assessment properly may include unnecessary bias.

Authors’ response:
The SIGN checklist assesses the same domains as NOS for both cohort and case-control studies. There is an assessment in selection bias, assessment of outcome/exposure status and whether the two groups are comparable. SIGN has the added advantage of assessing statistical significant of a result and the risk of chance. In addition, SIGN assesses whether exposure/outcome status or case definition is ascertained in a validated method, which provides additional confidence in the quality of studies.

As there are currently no consensus guidelines recommending a particular tool for quality assessment of observational studies, we chose to use SIGN over NOS in particular, because the topic of this systematic literature review was clinical in nature and SIGN is targeted towards guideline development therefore contains questions for clinical considerations.

When we refer to ‘general’ population in our paper we do not mean a general population overall or average in the community. Instead, we refer to a general population of antipsychotic users (i.e. instances where the authors do not differentiate the indication/reason for antipsychotic use) and therefore the population of AP users may be a combination of patients with schizophrenia, bipolar, dementia, etc.

4. The study included conference abstracts. Although it is true that both published and unpublished results are available, mitigating concerns of publication bias, the study did not mention how many conference abstracts were used and the results of quality assessment.

Authors’ response:
We included only 1 conference abstract. (Wang et al., 2014) with the accompanying quality assessment (eTable 4). We have included a sentence in the manuscript (page 8 under Quality Assessment) to describe the quality assessment of this abstract. To ensure rigor – we contacted the primary author during the data extraction phase to confirm the data extracted.

5. Among included studies reported antipsychotics and MI risk, the most recent year of publication is 2015, but did not show more evidence as compared with two previous studies of meta-analysis (Yu et al., 2016, and Huang et al., 2017; J Psychopharmacol. 2017 Dec;31(12):1544-1555). So what is really new?

Authors’ response:
As with primary studies, findings from systematic reviews can differ, depending on the methodological approach adopted by reviewers and the quality of the review. It is therefore important that we do not rely on the findings from just single review studies when reviewing evidence, including whether there is an association between antipsychotics and MI risk. Although we identified the same studies as in Yu et al, we draw different conclusions. Our conclusions are justifiably much more cautious than those of Yu et al. The authors of the latter article conclude quite firmly that antipsychotic drug use is associated with increased risk of MI. Our review urges far more caution and highlights the need for further and more rigorous methodological studies. The need for further research in this area should not be understated or dismissed. The review by Huang et al was performed concurrent to our review and published after the completion of our review – it is not uncommon for multiple reviews on the same topic to be published within a short time of each other. Huang et al’s conclusions are in line with our own conclusions and also differ to those of Yu et al. Given the contrasting conclusions of these two existing review, we believe our own review makes an important additional contribution, adding further support to the conclusions drawn by Huang et al, and further impetus for the need for more research in this area.

We have referred to the review by Huang et al in our introduction (page 5, paragraph 1, lines 13-15) and in the discussion section (page 13, paragraph 1, lines 22-24 and page 14).

6. In discussion, the authors mentioned “more detailed and comprehensive search strategy.” However, it may be resulted from misunderstanding confounding adjustment, comparison group, antidepressants and antipsychotics, and misusing a tool of quality assessment. The authors further criticized the previous meta-analysis (Hsu et al., 2017) “appeared to have pooled studies irrespective of study population, study design and type of effect estimate,” and “pooling together different study designs and different effect estimates is methodologically inappropriate and can result in misleading findings.” Nevertheless, the previous meta-analysis conducted subgroup analyses of the elderly population, dementia population, population-based studies, and case-control studies. I am afraid that I cannot agree with what the authors criticized in the discussion. The authors may need to scrutinize the previous meta-analysis again.

Authors’ response: Whilst the previous review did perform some sub-group analyses by population type, within these sub-group analyses they still included either: methodologically different study designs; or different effect estimates. For example, when pooling together studies on dementia, they pooled hazard ratios and odds ratios together (which are not equivalent), which can lead to inappropriate and misleading summary estimates.

We also identified many more relevant studies which were not mentioned in the review by Hsu et al and so we do not believe that these studies were excluded in the previous review on grounds of study quality. Whilst Hsu et al did exclude some studies, they did not provide the references for these in their article.
Regards the reviewer’s comments on quality assessment, it would actually be methodologically inappropriate to exclude observational studies on the grounds of study quality (because it can be difficult to distinguish whether authors failed to meet a specific quality criterion or simply didn’t provide the necessary information to allow assessment of that criterion). Instead, a discussion of study quality and implications for interpretation of findings is the recommended approach.

7. In 2016, Yu et al. published a meta-analysis of antipsychotics and risk of MI. I do not see much discussion. The authors mentioned “this previous review identified the same studies and included sub-group analyses, they combined results from different study designs or study populations and often pooled different effect estimates, which affects reliability and interpretability of pooled results.” However, the authors did not explain why they included different studies seeing that the two meta-analysis indeed have the same period of included studies. I did not find this simple sentence was not persuasive.

Authors’ response: We think the reviewer has misunderstood this section. We found almost the same studies as Yu et al, identifying two additional studies published since that previous review. We have explicitly highlighted this in the discussion section, page 14, paragraph 1, line 3. The period of study inclusion between the two reviews is not actually the same (our review includes two further years of searching). By ‘different’ studies, we mean that they pooled together methodologically different studies. We have amended the sentence on page 14, paragraph 1, lines 3-7, to clarify this point.

The authors did not quoted “Huang et al., 2017; J Psychopharmacol. 2017 Dec;31(12):1544-1555.” Huang et al., 2017 found that antipsychotics was associated with an increased risk of MI (pooled OR, 1.55; 95% CI, 1.33–1.79 compared with non-use) based on 10 observational studies. Zivkovic et al. presented inconsistent results, and failed to show any evidence that this study is more robust than the previous two.

Authors’ response: We have now included a discussion of the review by Huang et al, which includes the same studies as in our review. Please see our response to your comment number 5 above, which includes a detailed response related to this point. A key point here is that the conclusions drawn by Huang et al are actually consistent with our own review conclusions and differ from those of Yu et al. In line with our findings, Huang et al conclude that due to considerable heterogeneity and methodological limitations, we cannot draw firm conclusions about the associations between APs and MI risk. Like us, they highlight the need for further studies in this area.

8. Abstract
The authors succinctly summarized data sources in the abstract, but they did not include years searched, which should be addressed in the abstract.

Authors’ response: We have added this to the abstract (methods section, first line).

9. Abstract, “In particular, their effect on risk of stroke and myocardial infarction (MI) remains unclear.” I don't think there is any doubt that antipsychotic agents increase the risk of stroke, so that it is misleading to say "remains unclear."

Authors’ response: We believe that uncertainty around the effect of antipsychotic agents on risk of stroke does persist, given the methodological limitations of most existing studies in this area. As we
point out in our article, the lack of control for confounding by indication is a major limitation which affects the conclusions that can be drawn from many studies. Whilst there is evidence from some studies that antipsychotic drugs may be associated with increased risk of stroke, the evidence is far from consistent across all studies and population sub-groups. We have therefore amended the sentence in the background of the abstract to clarify this point, which now reads: “The effect of antipsychotic (AP) drugs on risk of stroke and myocardial infarction (MI) remains unclear, due to methodological limitations of, and inconsistencies across, existing studies”

10. In conclusion, the authors included studies that did not fit their inclusion criteria. They misunderstood confounder, confounding adjustment and risk effects of confounders in population-based studies. The study incorrectly included antidepressant agents in the meta-analysis. The study did not use an appropriate tool of quality assessment. Hence, the results and conclusion are misleading. Unfortunately, revisiting the protocol and reviewing all potential relevant studies may not correct the mistakes, since there are not enough new observational studies to add more evidence currently.

Authors’ response: We believe we have addressed these concerns in our rebuttal and in our revision. We would also like to reiterate that this review adds a substantial new number of publications for stroke (19 versus 10 in the previous review), in particular identifying far more cohort studies (8 versus 2) than identified in Hsu et al.) Whilst this review may not add a substantial number of new studies on MI compared to previous reviews, it does make important contributions in terms of: how the existing evidence should be interpreted; the conclusions that can be drawn; and highlighting the need for further and more methodologically robust studies in this area.