Reviewer’s report

Title: Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: A systematic review and meta-analysis

Version: 0 Date: 02 Feb 2019

Reviewer: Ioana Cristea

Reviewer's report:

I was a Reviewer for the protocol of this report. I am content to see the authors carried this project through, and I believe the topic is relevant and the authors have worked very hard for this research. However, this is a complex and ambitious systematic review and meta-analysis, and at this point the methodological part has many gaps and is not adequate in this form. It would need to be substantially revised before I can assess the reliability of the results. I tried to detail several points that need to be addressed, some of them entailing substantial modifications.

Abstract:

I assume Comprehensive Meta-analysis is the software used: there is no need to mention it in the abstract. It would be better to use the space to specify which type of effect size (ES) was used and how was it calculated (see comments about statistical analysis).

p. 4, l 19-24: Please re-organize the inclusion criteria to make it clear which is the Population, Intervention/Comparator (none in this case), Outcomes (including the types of instruments that are eligible, with examples) and study design (as it is specified now). The way the criteria are presented now, it's not clear eligible studies have to meet them all.

Exclusion criteria also need to be made clear. Why were only articles in English eligible? How did the authors handle cases where the sample was mixed (both adults and young populations) or where there were no specifications of age?

Regarding diagnosis, the authors need to clarify how did the selection work for subclinical or related versions of the disorders. More generally, based on what diagnostic manual did the authors identify these disorders and why only these three strict diagnoses and not also other disorders in the same category (e.g., other psychotic disorders). Here too, it needs to be made clear what happens in case of studies with mixed samples (e.g., studies on severe mental disorders that combined psychotic and bipolar patients)? In what case, if any, were they eligible?

For instance, were only studies on major depressive disorder/MDD eligible (i.e., no studies conducted on depressed participants that did not have a formal MDD diagnosis) and if so, how did that have to be diagnosed for the study to be eligible (i.e., was only a diagnostic interview acceptable, such as the SCID, MINI, others or was it also acceptable if participants were selected based on high scores on a clinical scale, such as the Hamilton Rating Scale for Depression). Why were other psychotic disorders aside from schizophrenia (e.g., schizoaffective) not eligible? Again, how did participants have to be diagnosed in order for the study to be consider eligible. Were both types of bipolar disorder eligible and if so, why was cyclothymic disorder also not eligible?
Finally, were studies where participants had one of the disorders of interest associated with a general medical condition or use of medication or a substance eligible?

p.4 l.9-10: All searched databases need to be mentioned. Further down (p.5) the authors mention non-peer-reviewed sources; this needs to be stated here with details regarding what types of documents were eligible (e.g., reports, conference abstracts, dissertations) and where exactly were searched?

p.4-5: I don't understand whether studies had to report the prevalence and associated factors in the abstract. Some studies might just include some of this information in the full-text, so it is too restrictive to select in this way. Also, "associated factors" is vague, how can another reviewer implement this selection filter? In this stage, the authors should have selected any study that was potentially eligible for the full-text selection phase.

Also, why did 2 reviewers re-assess the selection and how? What does it mean the body of the study was assessed? The optimal procedure would have been to have reviewers work independently so as not to influence each other.

p.5: The concept of "associated factors" the authors mention throughout is vague, it needs to be clearly defined with stating what categories of factors were available and giving examples in each.

p.5 l. 9-10 Why were studies that considered psychiatric disorders as a factor for non-adherence excluded a priori? Was this decision carried forward even if these studies also reported on other non-adherence factors? This decision needs to be justified and moved with the exclusion criteria.

p.5 l. 7-9: In the cases of studies that did not report sufficient data, why were these excluded before the authors could be contacted to provide the data? I advise the authors to reconsider this decision.

p. 5 l.14-16: If non-peer-reviewed sources were included, the authors need to state where and how they searched for this?

p.5. l. 18-19: More details need to be given as to what was rated with the Newcastle-Ottawa Scale, any modifications/adaptations of parts of the scale for the types of studies included, and how were disagreements resolved.

p.5. l. 19-20 This phrase is superfluous, we start with the assumption all authors of systematic reviews always do this.

The statistical analysis section is insufficient and need to be dramatically expanded with more details. First, the authors need to state what happened with studies that had multiple measures of adherence (was one selected and on which criteria? were they combined), as well as with studies that reported data in subgroups and not on the whole sample? The authors need to state what was the ES indicator used and, since this is a more complicated type of meta-analysis given it pools proportions, what method was used for the construction of confidence intervals, which is a non-trivial problem for a meta-analysis of proportions. The authors should look into methodological papers for meta-analyses of prevalence such as the relevant sections in the Cochrane handbook (section 9.4.8) and https://jech.bmj.com/content/67/11/974 The software the authors used is quite limited for a meta-analysis of prevalence. I advise the authors look into other options such as STATA or R.

It is insufficient to say inspection of small study effects (a term that is preferred to publication bias) was done by inspection of the forest plot. What was inspected? Also, it would be recommended the
authors use a statistical method to evaluate the existence of small study effects. The authors would need to check the literature for an adequate method given the nature of their data (binomial), e.g., Egger's test and other methods for continuous data are probably not acceptable.

What model was used for subgroup analysis and what restrictions were in place (i.e., how many studies had to be available to perform them)?

Results:

Table 1 is completely unreadable. Please re-organize/condense information, use abbreviations (to be explained in a note at the bottom of the table) or if necessary, break it into more tables.

The search is over an year old and should be updated.

How were associated factors studied? The authors mention significance in relation to associations all throughout the Results section, but there is no indication as to how were these factors assessed statistically or if the authors are just tabulating statistically significant results from the primary papers? The fact the authors stated they would only conduct one subgroup analysis (p.5-6) makes this entire portion of the results even more confusing. As I mentioned previously, we would also need to know exactly which these factors are, and how was their impact gauged.

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Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

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No