Author’s response to reviews

Title: Psychotropic medication non-adherence and associated factors among adult patients with major psychiatric disorders: a protocol for a systematic review

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Author’s response to reviews:

Cover Letter
Date: 03/10/2017
To: BMC systematic review Journal

Subject: Submission of revised version manuscript (SYSR-D-17-00186)

First of all, we would like to thank both of the reviewers and the editor for the effort you made to review and forward your input into our manuscript. We are glad to inform you that we have made the revision on our manuscript as per the journal guideline and reviewers comments entitled “Psychotropic Medication Non-adherence and associated factors among Adult Patients with Major Psychiatric Disorders: a Protocol for a Systematic Review and Meta-analysis: Agumasie Semahegn*1,2, Kwasi Torpey1, Abubakar Manu1, Nega Assefa2, Gezahegn Tesfaye2, 3, Augustine Ankomah1. We tried to address all the comments and also add some revision by ourselves and arranged our response in track change format to make more visible. We organized the submission into two separate files (main revised manuscript and track change manuscript as supplementary for visibility of the changes we made). So we would like to kindly request to consider our manuscript for publication. In the meantime, we are so delighted to
receive any further comments for the betterment of our manuscript. Do not hesitate to ask us if you have any inquiries!

With Kind Regards!

Point-By-Point Response

Psychotropic Medication Non-adherence and Its Determinants among Adult Patients with Major Psychiatric Disorders: a Protocol for a Systematic Review and Meta-analysis

Agumasie Semahegn, Ph.D. student; Kwasi Torpey; Abubakar Manu; Nega Assefa; Gezahegn Tesfaye; Augustine Ankomah

Systematic Reviews (SYSR-D-17-00186)

Reviewer reports:

Reviewer #1:

Overall, the authors should significantly restrict the focus of their meta-analysis and describe the conditions they are focusing on, the types of drugs and why they were chosen. Psychiatric conditions and drugs have very different effectiveness to adverse effects profiles, assessing non-adherence across them leads to results which are impossible to interpret. A lot of general and vague information is presented, in the detriment of specific information related to the review.

Response: thank you for the comment. We tried to make the protocol simpler and clearer for readers.

There are numerous wording and grammar errors in the text. The abstract at least should be revised, as it is difficult to understand. I do not understand what determinants the authors are looking for, there can be many factors for medication non-adherence. Specifying Word and
Excel will be used is a waste of abstract space, the authors should instead give more data about the actual planned analyses, which they describe very generally. PRISMA is a reporting guidelines, so again stating in the abstract that it was used is superfluous.

Response: Thank you! We have done revisions to correct typos and grammar errors. To make simpler, we have replaced “determinants” associated factors that included individual related factors, family or community or social support related factors, attitudes, medication side effects, health system factors. We are not trying to be concentrated on specific factors. Reading to excel and PRISMA, we kindly omit in the abstract section as per the comment.

Introduction:

* The authors dedicate a whole page to arguing that psychiatric disorders are a problem. This is already widely-known and this section is superfluous.

Overall, I did not manage to understand well what the authors want to study. Moreover, non-adherence is a concept that does not have much relevance if it is studied in general. Psychiatric disorders and medications are widely different, adherence to lithium is in no way similar to adherence to anti-depressants. I also don't see the link between non-adherence and increased burden of disease; for many of these conditions, the issue is that treatments are not effective. How would it help to be adherent then? For others, the issue is that there are serious side-effects, and like in all domains of medicine, the patient can hardly be blamed that the balance of side-effects to benefits is tipped toward the first one.

Response: thank you for the comment, we have done a lot revision to make our work clear and simpler for readers. We do think this systematic review and metanaysis work is very important and will give a strong evidence on multifaceted associated factors of psychotropic medication non-adherence. We are sorry for what you said that “does not have much relevance if it is studied in general”. We have planned to cover all associated factors, and it is not medication or drug specific. Medication side effect is one specific factors but we will tried to address family or social support factors, individual attitude towards medication, patients insight, health system factors and other individual related factors etc. Regarding to the link between increased burden of disease………patients with major psychiatric disorders with medication non-adherence can cause exacerbation of their psychiatric illness and complications which leads psychiatric re-hospitalization, poor psychosocial outcomes, relapse of symptoms, reduce effectiveness of the treatment, waste of limited health care resources, increase substance abuse, poor quality of life and increased suicide (3, 10, 11, 15–18). Recurrent relapse of symptoms may be less responsive
to subsequently administered medications and causes poorer psychiatric functioning, impaired occupational functioning, interpersonal difficulties and higher health care costs (17,18).

* The authors present some adherence rates but there is a wealth of literature here, by disorder and the authors should synthesize this literature and certainly not cite an unpublished dissertation (reference 3). The authors do give some sparse references from various disorders, but once again non-adherence does not have the same causes and even consequences across psychiatric disorders. Again, the link between medication non-adherence and negative consequences of many psychiatric disorders is far from clear, not similar across disorders and I believe in some cases not even existent.

Response: Thank you for the comment. We would not say medication non-adherence have same cause. We planned to synthesis and look for associated factors in different dimension and perspective as much as possible to generate strong evidence and dig-out deep-rooted causes to psychotropic medication non-adherence.

• Search strings

stating search strings will be created based on the research question (p.8) offers virtually no information. I understand the authors don't have the search string, but at least some key words can be indicated. What is a sample search string? Are those key words that will be used? If yes, the number of records identified seems enormous. How do the authors plan to handle this? The shorter Pubmed string that identifies 625 records has the problem that the authors use just some synonyms for determinants, I suspect many will be hardly ever uses (associated factors/influencing factors, appearing in this phrasing, or even determinant, which is a very causal term), and others that are not in the search string (prognostic, predictive, correlates) will be widely used. This string is probably going to miss a large number of relevant records.

Response: thank you for the comment. We have made revisions and also the search string that we put as supplementary material is not the final one. It will be updated and modified as necessary. In the meantime, we are continuously amending the search strings and tried to make comprehensive. Look at additional file 1 searching on progress. Thank you for the look!

• What will be included as psychiatric disorders and what rule will be used?

Also what do the authors planned to do with the many pooled analyses (more trials combined) or secondary analysis of trials that often look ad adherence?
Reponses: we are interested on three common psychiatric disorders (schizophrenia, major depressive disorders and bipolar disorders). We will only concentrate on observational studies. We did not mention trials in our manuscript, in which we are not evaluating trials effect. our plan is pool the magnitude of different primary studies to estimate the pooled non-adherence level and synthesis literatures to identify associated factors, and also pooled subgroup analysis for schizophrenia, Major depressive and bipolar.

* Screening studies based on whether data for the meta-analysis is included in the abstract is insufficient, this will miss the studies where this data is only reported in the paper.
Response: Thank you for the comment. We will consider conference abstracts, and also we will try to access the full study report as much as possible.

* The AMSTAR is a tool for rating the quality of meta-analyses, how can the authors apply it to their papers?
Response: Thank you for the comment, we kindly take the AMSTAR out from the quality assessment tool as per the recommendation.

The definition of outcomes is very general. Studies are likely to have defined adherence in different ways. What definition will the authors use? Whatever the original authors give? The authors then say they will also use other indicators like non-compliance and drop-out, how will they be used? Will they be considered equivalent to non-adherence? If yes, they should also be in the search strategy.
Response: Thank you for the comment. We will use synonyms or alternative terms such as non-compliance, drop-out as equivalent to non-adherence, and also we are delighted to include in the search strategy. Thank you once again.

Are the authors interested in testing any moderators? Particularly since they have such a large and poorly defined topic, spanning different disorders and treatments, heterogeneity is bound to be a problem and moderator analysis are one possible way to explore that.
Response: Thank you for the comment. We will use moderator analysis to handle variabilities due to over sample and by disorders categories. We thought that subgroup analysis is one of the moderator (see page 11, line 14 and 15). In addition we will consider sample size difference on
the pooled estimate, however, we will use random effect model which used weight method (see page 11, line 12 and 13).

Overall many things in this protocol are very vague. The authors just state they will do everything but give very few specific details. For instance, how will study quality be rated? What items will they focus on? Which scales will be used by type of design? The measure of effect size is not specified. What quantitative data will be extracted from the selected papers and how will they be used?

Response: we thank you for the comment, we have drafted the criteria of quality assessment and included as additional file 3.

What will the authors do with overlapping data, for instance when several of included articles will have overlapping samples?

Response: Thank you for the comment. As far as the studies conducted in their own context and different setting we will included in to the review process as per the eligibility criteria. On the other hand, if the overlapping samples or data (for example the sub analysis from same database or source) and the findings are identical, we will only include the one which had the most representative sample and recently published one. But in case of duplicate files, only one will be consider for the selection process.

• There should also be some quantitative way of assessing publication bias. I also don't understand what it means that publication bias will be anticipated based on p values smaller than 0.10 (p 12, l.20-21).

Also, what does high heterogeneity mean (p.12, 1.26-27) exactly? Over what limit will the authors not conduct a meta-analysis.

Response: Thank you for the comment, we will inspect the funnel plot for potential publication biases. We kindly omitted the p values. Regarding to the heterogeneity, if the I2 > 75%, we will consider there is high heterogeneity between studies. We really thank for the comment!

Only one subgroup analysis is planned? The class of drugs is not even mentioned as a potential moderator, but some drugs have more side-effects and this can lead to non-adherence.
Response: Thank you for the comment. Yes we planned subgroup analysis for type of psychiatric disease. We tried to be focused on the three psychiatric disorder (schizophrenia, major depressive disorders and bipolar disorders). We will not do medication (drug) specific adherence. Thank you so Much!

Reviewer #2:

Thank you for inviting me to review this protocol which aimed to estimate the level and identify determinants of psychotropic medication non-adherence among adult patients with major psychiatric disorders. The review will be an important contribution to understanding psychotropic medication adherence in low and middle-income countries. The protocol is well-written. However, there are some issues that the authors need to consider in revising this manuscript.

Revise the background section as it contains irrelevant details.

Methods: HINARI is not a search engine, it is a way to access full text for low and middle-income countries. Rather, you may consider searching literature in African Index Medicus and other sources from low and middle-income countries.

Response: Thank you for the comment; we kindly out HINARI from the list as per the recommendation.

• You mentioned that you will search studies before August 1st, 2017. Why? If the electronic search is already completed, it needs to be updated.

Response: thank you for the comment, we planned to the search until then while submitting the protocol to the journal, but we are still working on the searches. So we are delighted to update the date until the end of December, 2017.

The introduction section is poorly structured and has too many redundant arguments which made it less interesting to read. Example: line 3-6, 11-14 of page 5 was already described on page 4.
The same information which was described is explained again and again on subsequent pages. It needs to be shortened and restructured.

Response: we thank you very much, we omitted some redundancies as per the recommendation.

Methods: on line 13 to 15 of page 6, it was mentioned that the authors will contact potential authors in case they have publications on the topic. How do you select these people? How do you trace their profile?

Response: we thank you, yes, we have a plan to request authors for more studies, we will select authors whose studies will be selected and included to the systematic review. We will search by the reference as well as request authors if we will be able to access their email on their articles.

The phrase "Low and middle-income countries" needs a proper definition and should be part of the keyword search.

Response: we kindly omit this phrase. Thank you for the comment!

The authors mentioned they will use AMSTAR to assess the quality of studies. AMSTAR doesn't help you here. AMSTAR is a methodological assessment tool for systematic reviews. It cannot be used for evaluating the quality of observational studies. Explore which other tools are appropriate for your research question: CASP, Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the NIH, Newcastle-Ottawa scale, etc.

Response: Thank you for the comment, we kindly take the AMSTAR out from the quality assessment tool as per the recommendation.

It increases the quality of your review if two authors screen titles and abstracts and full texts independently, if not possible at least a sample of the titles and abstracts and the full texts screened by one author should be reassessed by another one. Then possibly, you can look at the level of agreement.

Response: we thank you for the comment.

Consider rewriting page 10 line 1-8. It is not clear.

Page 10, line 7 to 8: please mention the criteria
Response: thank you so much we have done a lot rewritings and revisions.

Data Extraction: It is also important to extract data about the tool used to measure adherence. The tool is important if authors intend to combine estimates of adherence.

Response: we thank you for the comments.

On page 11 line 7-8, the authors mentioned publication bias will be assessed by visual inspection of funnel plots based on p values less than 0.1. Visual inspection of funnel plots doesn't provide p values.

Response: Thank you for the comment, we will inspect the funnel plot for potential publication biases. We kindly omit the p values. We really thank for the comment!

On the same page, it was mentioned that if heterogeneity is high, narrative synthesis will be preferred. How high? Methodological, clinical, statistical heterogeneity?

Response: We will consider high if I² >75%.

On page 11 line 12-14, the authors mentioned they will have meta-analyzed estimates with a similar set of confounders. This is not clear. To identify determinants, will you also pool OR, RR? None of such information is described in the protocol.

Response: We thank you the comments we will compute the pooled estimate of the medication non-adherence, and also we will narrative synthesize the associated factors as per their theme (individual factors, attitude, family and or social support, patients insight, medication related factors such as side effect, duration, and health system factors).

Discussion: The discussion needs extensive revision. It is poor in its present form. It is a repletion of what is already written in the introduction.

Response: we accepted and modified as per the comments.

Minor comments:

Microsoft Word is not a good choice for data extraction. Use excel as it offers a large volume of data collection for each study.
Response: thank you so much, we kindly omit Microsoft word, however, we are saying that we will describe included studies characteristic using Microsoft table.

Change the word articles to "studies"

Response: Thank you we accepted and changed “articles to studies”

Thank you so much!