Author's response to reviews

Title: Sub-threshold depression and antidepressants use in a community sample: searching anxiety and finding bipolar disorder

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Author's response to reviews:

To: Editor
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MS#:

Dear Editor,

Thank you for the reviews on our recent manuscript submitted to BMC Psychiatry. Please find enclosed our revised manuscript entitled “Sub-threshold depression and antidepressants use in a community sample: searching anxiety and finding bipolar disorder”. We found the comments by the three reviewers very helpful and the revised manuscript includes all their suggestions. Below, we have responded to their specific critiques and pointed out the revisions made to the manuscript. We hope that the work is now acceptable for publication.

Response to reviewers comments

Reviewer: Prof. Angermeyer

Critique 1: In the Abstract, the assessment of the lifetime prevalence of hypomania in sub-threshold is mentioned as one of the objectives of the study. However, no relevant information is provided in the Results section (or did I miss it?)
Response: The lifetime prevalence of hypomania and mania detected by MDQ is now given in the results section. A table is also added which describes the prevalence of SD (note that we have changed STD into SD to avoid confusion), the prevalence of mania and the comparison of mania between SD, DE and in the overall sample without any depression.

Critique 2. In the Tables, the meaning of some of the figures shown is not sufficiently explained. For instance, in Table 1 it remains unclear what the figures provided under the headings “male”, “female” and “total” indicate. Same with Tables 2 and 4. In Table 3, “Receipting by psychiatrist” and “DOC” need explanation.
Response: We have now revised the tables with better explanations.

Critique 3. The Discussion would benefit from adding a paragraph on limitations of the study. For instance, the question of representativeness of the findings for the whole of Italy may be addressed.
Response: A point well-taken, and a section with the limitations of the study is now added in the revised manuscript.

Critique 4. There are some spelling mistakes which need to be corrected.
Response: We have carefully proofread the manuscript now and also have improbe the language.

Reviewer: Prof. Campos
- Major Compulsory Revisions

1- INTRODUCTION:
Critique: The authors refer to the evaluation of the lifetime prevalence of hypomania but it is not shown in the results section.
Response: Please refer to Response to Critique 1 above

2- METHODS
Critique: Recruitment methods and study sample:
The sample should be described in details, including inclusion and exclusion criteria. It is not clear if Bipolar Disorder patients were excluded and what is the ND group.
Interview, tools and study assessment:
In the text, MDQ indicates the presence of a mood disorder. Once MDQ is a screening tool it should be detailed if the authors considered it to make a diagnosis of Hipo/Mania and it relation to the ANTAS findings.
Response: Points well-taken. We have made the following changes in the revised manuscript.

Under Methods section, we have now defined the terms in page 6. Note that we have changed STD into SD lest the term might be confused with sexually transmitted disease. We have also pointed out exclusion and inclusion criteria and clarified about BD and ND.

Similarly, under Interview, tools and assessment, we have also discussed now the diagnosis of Hipo/Mania and its relation to the ANTAS findings.

Furthermore, we have also discussed these issues in detail under the Discussion section (page: 10). In any case, we have taken into account that the fact that the diagnosis by SCID may be too restrictive and therefore we used the MDQ positivity also to measure the “bipolarity spectrum” in people with Depressive Episode. The recognition of Bipol Disorder in people with Depressive Episode is not the objective of this study and this topic was addressed by another study using the same data bank (Carta et al. J Affect is Submitted).

3- DISCUSSION

Critique: It should be discussed the limitations of using HAM-D as a diagnostic instrument.

In this section the authors considered that MDQ detected a previous manic or hypomanic episode. The limitations of using this definition must be described.

Response: We have pointed out in the discussion section that the definition of SD as having HAM-D score more than 10, which is an operational choice for detecting people with a relevant depressive symptomatology that may lead to an antidepressant use without any descriptive limitations.

Moreover, we have now also discussed the limitations in the use of MDQ as screening instrument for mania.

Minor critique: We have also reorganized the tables in the revised section.

Reviewer: Prof. Gandotra

1. Major compulsory revisions:

Critique: The hypotheses posed by the authors are well defined but the subsequent clarification in the results and discussion appears to be lacking. The authors also propose to assess life time prevalence of hypomania in these subjects. The text of the manuscript does not appear to mention anything regarding this observation. The tables do not highlight any figures for this finding.
Response: We have now pointed out and discussed the lifetime prevalence of hypomania and mania detected by MDQ in the results section. We have also added a table with the prevalence of SD, the prevalence of mania in SD and the comparison between mania in SD, DE and in the overall sample with no depression. We hope that this would suffice.

Critique: The methodology is sound and data acquisition has been adequate. Yet if we see the relatively wide confidence intervals for the findings on the sub threshold depression, the strength of the finding still appears relatively weak.

Response: Under the limitations section we have indicated that the prevalence rate of SD is quite low and thus the results need to be further confirmed. On the other hand, only some of the data have large intervals but not all. Nonetheless, the totality, when taken into account suggests that the results are sound. We have clearly pointed these out now in the revised manuscript.

Critique: The manuscript appears to have focused too abruptly on the STD itself without providing the details of the large sample from which the STD was derived. It appears from the Table 2 that many subjects of the total sample happened to use antidepressants of all classes even when they were not found to have either a DE or STD. It is unclear as to for what reason they were on antidepressants. The co morbidity data on these subjects is also lacking and appears confusing.

Response: This paper is one of the papers derived from this national survey. This current paper is focused on mania and antidepressants in SD, one of our previous papers (Carta et al. 2010) was on antidepressants in Lifetime Major Depressive Disorder (we have another paper in preparation on Bipolar Disorder). We used the Depressive Episode Point prevalence because a large amount of the current literature is focused on the difficulties for the clinician to identify manic/hypomanic episodes in a depressive episode. Thus, we think that from a public health point of view, determining how many people in the community in a given moment suffer from a depressive episode and how many of them have manic/hypomanic lifetime episodes, is quite important. Measuring the point DE prevalence and the percentage of those in this category having a lifetime-comorbidity with a Manic/Hypomanic episode is important. Our finding that under estimation of manic/hypomanic episodes in SD and that there is an increased risk for it with the use of antidepressants is also significant.

Furthermore, we have used an operational definition for SD (a score of >10 HAM-D) for identifying such patients. In Table 2, we had to point out that a large number of people who had a past depressive episode but currently do not have any symptoms of depression are still under antidepressants treatment. The way our study is designed, these people are in the ND group. A classification of ND does not mean the subjects never had a depression episode in the past, but simply that they do not have any depression at the time of the interview.

Finally, we used the co-morbidity data for anxiety only in order to explain the use of antidepressants in SD; for GAD, DOC and PD, treatment by antidepressants is
indicated. Thus, this paper in not necessarily focused on co-morbidity and therefore the restricted use of co-morbidity in the study.

Critique: The data on the use of antidepressants reveals the use of all categories of antidepressants (TCA, SSRI, bupropion, MAOI and also benzamides and psychotherapies). The authors conclude that there needs to be a caution in the use of antidepressants in subjects with STD. The caution is appropriate in line with the recent literature but however, it is questionable if it is so broad to include the benzamides, quetiapine, psychotherapies, and hypericum etc. The findings would have been better highlighted for the use of core antidepressant class of drugs alone.

Response: We thought that it would be better to include all categories so that the study will not highlight only a core group to avoid any potential misleading of the findings. However, we have pointed out that there should be caution in the use of antidepressants in subjects with SD, particularly those antidepressants with higher risk for inducing mania. This should mitigate some of the above concerns. We also have now discussed some of the limitations of the study under limitations section. Hope this would suffice.

Critique: The authors do not cite any limitations of the study.
Response: We have now added a section on limitations of the study.

2. Minor Essential revisions:
Critique: There are some grammatical errors in the manuscript. The first line of the introduction “Patients with mild-to-moderate, chronic or episodic dysthymia and anxiety may are not benefit greatly from antidepressant treatments”. Dysthymia on pg 6 is misspelt. Line on pg 7 reads as “thus the real factor for assuming antidepressants is the anxiety disorder and MDQ positivity is probably occurring as a confounding factor”.
Response: We have corrected this problem and have rewritten this section.