Author's response to reviews

Title: Antidepressants in the treatment of depression/depressive symptoms in cancer patients: a systematic review and meta-analysis

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Author's response to reviews: see over
Cover letter

Reviewer's report:

1. This is an interesting study, but, even after the revision, I cannot see how the current study makes any significant contribution to the current literature. In addition, this article requires editing, especially with regard to usage of punctuation marks and articles. The authors need to verify their results listed in the body of the article and references listed at the end of article.

We revised the manuscript according to the suggestions of the reviewer. Therefore, we further clarified the contribution to the current literature and revised the used language. We show in the introduction that:

- Depression is an important issue for cancer patients, because of its impact on a) survival, b) quality of life

In the paragraph “treatment of depression in patient with cancer”, we show that:

- The results of the available RCTs are not univocal. This fact speaks for the need for a meta-analysis.
- The reviews can show an overview of the studies, but cannot quantify their effect, so that they cannot be seen as an alternative to meta-analyses.
- The meta-analysis of Rayner et al. included 25 RCTs with patients in the palliative care. A subgroup analysis for cancer patients (4 of the 25 RCTs) was not performed, so that the authors did not make any recommendations for this population.
- Iovieno et al. conducted a meta-analysis for the efficacy of antidepressants in patients with depression and co-morbid physical illness. A subgroup analysis of patients with cancers (4 RCTs) failed to demonstrate a significant effect of the antidepressants in the treatment of depression in this subpopulation.
- Hart et al. studied the effectiveness of psychotherapy and of antidepressants in treating depression in patients with cancer. The overall effect was positive and there were no differences between the two kinds of treatment. However, there are some limitations in this study:
  1. The authors identified only 4 RCTs
  2. The placebo group of a three-armed study (Musselmann et al, 2006) was used twice in their analysis. This can bias the statistics.
  3. The authors used the Hedge’s g estimator to quantify effects. This can lead to an overestimation of the clinical effect, as it takes into account every improvement of the depression scores, even the ones which are clinical irrelevant. The relative risk ratio (RR) or the odds ratio (OR) for clinical relevant improvements yields results of clinical relevance. Indeed such a measure would have yielded no significant overall effect of these 4 studies (we repeated the analysis with the available data for responders and non-responders).

These limitations warrants caution in applying the antidepressant subgroup findings to general clinical settings.

Taking these points into consideration, the current meta-analysis makes a unique and significant contribution to the existing literature. We further clarified the introduction in comparison to other reviews and meta-analyses (see Reply 2).

Further we followed by enlarge the suggestions of the reviewer of additional punctuation marks and revised the language throughout the manuscript.

Major Compulsory Revisions
Introduction-

2. Page 3 Line 8 to Line 12- If there are many studies who have tried to evaluate the efficacy of pharmacological interventions among patients with depression, why are the authors conducting the current study? Just explain it in 2-3 sentences without providing lot of details.

See previous answer.
We further clarified this in the revised Introduction:
“…Hart et al. [Error! Bookmark not defined.] found a significant effect on depression ratings in the subgroup of four pharmacological studies which was not significantly different from the overall effect of the psychotherapeutic trials. However, this analysis included one placebo group twice and used Hedge’s g to quantify the results, which may bias statistics in the pharmacological subgroup. The authors discuss as a limitation that changes in questionnaire ratings may have limited clinical relevance. Depressiveness even without manifest diagnosis of depression may have adverse effects on prognosis and quality of life in cancer patients (see [14]) and, therefore, these patients should be included in intervention trials and subsequent meta-analyses. To overcome the limitations of the previous analyses, the present systematic review and meta-analysis focuses on the event of clinical relevant symptom changes in depressed or depressive patients with cancer.”

3. Page 3 Line 18 to Line 20- I disagree with the authors because in my doctoral Thesis, titled “Mental Health and Mental Health Services Utilization of US Cancer Survivors and Their Spouses,” I have compared prevalence of depression between general population and cancer population. These are national estimates and well matched population. So, I would suggest authors to change their statement.

There is no disagreement between the reviewer and us with respect to the prevalence of psychological distress in cancer survivors. Therefore, we look forward to see a full publication of the mentioned study. However, the upcoming publication of the national guidelines for psycho-oncology in Germany will state that there is no difference of ICD-10 chapter F diagnoses in these populations. Therefore, even if also not published yet, we have to consider this point as still controversial. Furthermore, the epidemiological findings are not central to the present manuscript.
To further clarify the discussion, we refer to a paper by the reviewer, which suggests, that the survivorship may be accompanied by psychological distress and this fact is indicated by the increased use of psychotropic medications:

4. Page 4, line 34 until page 5, line 17- This paragraph gives me an idea that the current literature is limited in quantity and quality. But, it doesn’t convince me how the current study is going to address these limitations. So, authors need to work on that.

Please see also the reply to the first comment. We have to notice that the criteria of the Cochrane Collaboration for the evaluation of the quality of studies were set after the majority of the reviewed RCTs were conducted. These criteria are relative strict. For example, the last observation carried forward method for missing data is often used in practice and is considered to be a much more appropriate missing data imputation method than the completers’ analysis. However, both methods are evaluated as inappropriate by the Cochrane Collaboration. The limited choices “yes”, “no” and “unclear” are insufficient to detect such
essential differences among studies. We address this issue in the appendix of our study. A more detailed overview of this point goes beyond the scopes of our meta-analysis. “We used the Cochrane Collaboration’s tool for assessing the risk of bias. These criteria may be considered sufficiently strict.”

5. Page 5 Line 19- How do you define “depressiveness”?

Depressiveness refers to the whole spectrum of depressive symptoms, even the ones which do not fulfill the DSM-IV or ICD-10 criteria for a major depressive episode. We use this term as an alternative to the “depressive symptoms”. It is not an official diagnosis but it is often used by psychiatrists to stress the importance of subclinical depression. Elevated scores in depression scales are equivalent to “depressiveness”. We give the following explanation in the manuscript: “..., i.e. impaired mood had to be diagnosed by clinical criteria or relevant depression rating scales.”

6. Page 6 Line 1 to Line 3- Why have authors not included the limits described here in the inclusion criteria list itself?

We added some of the search criteria as fourth inclusion criterion. However, we must differentiate the search criteria from the inclusion criteria. The inclusion criteria are the conditions which the articles must fulfill in order to be included in the analysis. The search criteria have to do with the strategy which we follow in order to detect the articles with the fulfilled conditions. Additionally, we kept the search criteria as a separate section. “4. The studies were published in English in the time between 01.01.1980 and 31.12.2010.”

7. Page 6 Line 12 to Line 15. This information should be moved to Analysis section

In the Methods section, we created a new paragraph “Articles selection and review strategy”.

8. Page 6 Line 29- The authors need to briefly explain the roles of forest plot and funnel plot.

We further clarify why we included forest and funnel plots and their function. “Risk of publication bias was assessed using a funnel plot, i.e. a display of estimated study quality in terms of standard error and the reported effect size.” “A graphical display of the relative strength of each study is presented in the forest plot (Figure 2).” “The risk for publication bias (i.e. studies with small sample size are at more likely not to be published, if their effect is small to moderate) is assessed by means of the funnel plot, which displays the relationship between the sample size and the effect size of the studies. The standard error instead of the sample size is usually used in the Y axis.”

Results-

9. Page 6 Line 34- Can authors categorize these 29 articles into groups that depict the reasons for rejections? I think that would be helpful for reader to see why you reject them.

We describe the step-wise analysis of study selection more clearly now in the Results section.
“The electronic searches yielded 5959 references from MEDLINE and 1041 references (clinical trials) from the Cochrane Library. After the initial scanning of the abstracts, a total of 38 reports were detected that may relate to drug trials using anti-depressants. Based on the full-text of these reports, 29 of them were rejected since they did not reported RCTs on anti-depressant treatment in depressive cancer patients. From the remaining 9 RCTs, 3 studies were head-to-head trials, i.e. active drugs were compared with each other [i, ii, iii]. Thus in total 6 randomized placebo-controlled studies fulfilled the criteria for this meta-analysis [iv, v, vi, vii, viii, ix]. The complete list of the assessed trials is presented in Appendix A.”

10. Page 7 line 4 to line 8: This paragraph is confusing. It makes you think that authors rejected 3 trials from 9 trials that were finally selected. So, I would suggest authors to rearrange them.

In this paragraph, we highlight the differences to previous reviews. For example, Morrow et al. (2003) studied the effect of paroxetine in patients with fatigue (used as inclusion criterion) and depression (not used as inclusion criterion). In consequence, we obtain a more homogenous group of RCTs which allows them to draw conclusions more easily about the effectiveness of antidepressants in patients with cancer. We further clarified the wording in this paragraph and provide a complete list of the initially screened manuscripts (Appendix D): “Previous reviews and meta-analyses exhibited a larger diversity of study designs [Error! Bookmark not defined., Error! Bookmark not defined., Error! Bookmark not defined., Error! Bookmark not defined.]. For instance, we did not include 3 trials that had not depression or depressive symptoms as an eligibility criterion even though the primary outcome measure was improvement in depression/depressive symptoms [i, xi, xii]. Similarly, we did not include trials which tested the efficacy of antidepressants in preventing depressive symptoms in patients with cancer [xiii] or in patients with melanoma undergoing therapy with interferon [xiv]. Appendix D lists all the 38 trials, which were screened and the reasons for in- or excluding them.”

11. Page 9 line 4: I would suggest authors to state the comparison groups.

We clarified the text: “in the drug and the placebo group”

12. Page 9: Discussion should be titled Conclusion and vice versa

We followed the BMC template (“instructions for authors”): The Discussion section follows directly the Results section. Conclusions are stated last.

13. Page 11 line 12: Is it 10% or 15%? In the results section, authors mention that heterogeneity fell to 10% and here they mention that it fell to 15%. Please verify and be consistent.

We apologize and corrected the typo.
References-

14. Page 33 Reference #10- There is a typo in the title and the year should be 1984.

We corrected these typos as well.


