Author's response to reviews

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

Authors:

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Author's response to reviews: see over
I. Reviewer: Chong Guan Ng

1. It is unclear why the authors are repeating the meta-analysis while there are many prior similar reviews.

A meta-analysis has advantages in comparison to a review. Although the existing reviews suggested a positive effect of antidepressants, previous meta-analyses failed to consistently demonstrate it for cancer patients. Most reviews included RCTs, which refer to specific treatment strategies, e.g. prevention during interferon administration. Hart et al. combined the review of psychotherapeutic and pharmacological studies yielding also a high heterogeneity. We discuss this problem in the “introduction” and the “results” section. The present meta-analysis focuses on psychopharmacological treatment of depressiveness and depression in cancer patients. This has been identified not only to reduce quality of life, but even as risk-factor for disease progression (see Satin et al.).

2. Why the term „oncology“ was not included in the search term?

The applied search terms were patient centered. However we picked up the suggestion and additional 27 entries were obtained with the extension for oncology. None of them revealed a potential other RCT using antidepressant medication. We mention this in the revised methods (‘Exploratory extension of search terms (e.g. including oncology) did not yield additional studies.’) page 6, lines 4-5

3. There were only two independent authors to review the article, so I wonder how the authors handle if there were any discrepancies.

Articles were discussed in the group and another experienced clinician from this group was available to decide in cases of disagreement, i.e. Martina Haeck MD. We clarify this in the revised manuscript (‘In case of disagreement clinician experienced in psychooncological consil and liaison services was involved to mediate consensual decisions.’) page 6, lines 10-11

4. There are no exclusion criteria?

The exclusion criteria are now separately stated: ‘Antidepressants are often used for indications other than depression (e.g. fatigue, pain, hot flashes) in patients with malignancy. Thus we excluded all studies in which depression was a secondary outcome only.’ Page 5, lines 30-32

5. Studies involved children or palliative care we included or excluded?

No studies matching the criteria included children. General populations from palliative were not separately considered. We focused on clear-cut populations with cancer diagnosis. We clarified the inclusion and exclusion criteria in the method section. Page 5, lines 22-32

Discretionary revisions:

1. There are many irrelevant elaborations in the introduction.

The introduction was considerably shortened to about half of the text.
2. You want to consider including Ng et al. J. Affect. Disorders 2012 as one of your reference.

We included this relevant citation in the revised introduction. It gives also a more recent account on prevalence rates.

Page 3, lines 19-22, Ref. 6

II. Reviewer: RS Punekar

1. The whole introduction section should be rewritten to give a comprehensive background including current literature on following topics:

We revised the manuscript and follow closer the suggestions of the reviewer.

a) Prevalence of depression among general population and the cancer population.

The comparison of prevalence and incidence of depression in cancer populations and general populations is still disputed. Although depression rates are high in many cancer populations, there is no consensus as to a difference with general populations can be determined. The review by Ng et al. is one of the most recent accounts towards the prevalence of depression in cancer.

Page 3, lines 19-22

b) Impact of antidepressants on the treatment of depression among general population and the cancer population.

This again is a very interesting and important question. However the answer seems to be as unsatisfying as to the previous questions. Effects of antidepressant may or may not depend on depression severity. Meta-analyses suggest somewhat higher responder rates in depression concomitant with (other) chronic physical disorders (e.g. RR about 2 in Taylor et al., 2011). In light of the heterogeneity between the studies such comparison would need to be performed systematically and this goes beyond the scope of the current manuscript.

c) Factors affecting the impact of antidepressants on the depressive symptoms of cancer patients.

So far little data are available on this. Our analysis of heterogeneity addresses this issue. We present the finding in the paragraph Subgroup analysis in the results section and discuss it further.

Page 4, line 27 until page 5, line 17

d) Gaps in the current literature
e) How does the study fill this gap?
f) What are the research questions or aims of this study?

The last paragraph of the introduction now further identifies the gaps and addresses the approach how to fill these gaps. The research question is to analyze evidence whether antidepressants relevantly improve symptom severity in depression or depression in patients with cancer.
‘Previous qualitative reviews underpinned the lack of evidence of the adequate effect of pharmacological interventions in the treatment of depression in cancer patients. However, the reviewed studies were heterogenous as concerns the studied population (e.g. fatigue or pain as eligibility criterion and depression as secondary outcome) and the type of the drug applied (e.g. antidepressants, benzodiazepines, antipsychotics, psychostimulants, etc.). Only limited conclusions could be drawn from these reviews for the effectiveness of antidepressants in this population. A meta-analysis estimated the efficacy of antidepressants in palliative care (patients with cancer, HIV, COPD, etc.;). The overall effect of antidepressants was significantly higher than the effect of placebo. However, only four of the twenty-five studies included cancer patients. A subgroup analysis was not performed for each population of patients and thus no recommendation can be given for oncological setting. In another meta-analysis antidepressants were found to be effective in the treatment of major depression with a co-morbid physical illness (RR= 1.42, P<0.0001). Again only four RCTs could be included that studied cancer patients with a diagnosis of major depression and no significant effect of antidepressants on response rates emerged in this subpopulation (RR=1.26, P=0.19). In contrast Hart et al. found a significant effect on depression ratings in the subgroup of four pharmacological studies which was not significantly different from the psychotherapeutic trials. As a limitation the authors discuss that changes in questionnaire ratings may have limited validity. Indeed as confirmed by the meta-analysis by Satin et al., depressiveness even without manifest diagnosis of depression may have adverse effects on prognosis and quality of life in cancer patients. The present systematic review and meta-analysis therefore focuses on the treatment of both major depression and broader defined depressiveness in patients with cancer.’

*Page 4, line 34 until page 5, line 17*

2. The authors have failed to convince why is this study necessary and how does it contribute to the field. They have to emphasize more on these points.

The revised Introduction is now clearer towards the study aim. We analyze psychopharmacological treatment of depressiveness and depression in cancer patients. Also syndromes that do not lead to a diagnosis according to the diagnostic manuals have been identified to reduce quality of life and may be risk-factor for disease progression.

*Page 4, line 27 until page 5, line 17*

3. Please remove headings for each paragraph in the introduction. Most of the necessary information should be written cohesively and instead of breaking it down in so many parts or paragraphs.

We removed the headings.

4. The introduction has a lot of unnecessary information.

The introduction is shortened considerably. Still we consider it important to highlight the problem with diagnostic criteria and heterogeneity of the studies to clarify our choice of inclusion criteria.
Methods.

5. In the eligibility criteria the authors need to explain to the readers why does it matter whether depression is a primary outcome or a secondary outcome in the articles searched by the authors.

There are many trials which study the effect of antidepressants on pain, fatigue, cognitive symptoms etc. The primary eligibility criterion in these studies was the presence of pain, fatigue and cognitive disturbances respectively, which means that the presence of depression was not required. Thus not depressed patients are also included. The selective inclusion of a subgroup of these patients in our meta-analysis (the ones who were depressed at the onset of the study) could introduce a bias (e.g. correlation of depression with the primary outcome etc.). Therefore, it would render the sample not representative of the cancer population with depression and thus not comparable with the other studies.

6. My question to authors about searching for studies is why didn’t they include „antidepressants“ in their search terms.

We aimed towards higher sensitivity and lower precision in this first selection in order not to miss an appropriate study. In particular, we omitted any search term for therapy or treatment, which could reduce the search sensitivity. In this we followed the suggestion of the Cochrane Collaborative.

‘In particular, we omitted any search term for therapy or treatment, which could reduce the search sensitivity. This approach is suggested by the “Cochrane Handbook for systematic Reviews of Interventions” ‘

Page 5, lines 34-36

7. Statistical analysis is not well described.

We further enhanced the description of the applied methods.

a) What calculations were made using what formulas in MS Excel?

The applied formulas are standard approaches to calculate RR and variance in a logistic model. We feel that the explicit listing of the formulas would render the manuscript less readable. The formulas are listed in Borenstein et al. (2009).

For the information of the reviewer, we summarize the statistical approaches here:

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Total</th>
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<tbody>
<tr>
<td>Verum</td>
<td>A</td>
<td>N1</td>
</tr>
<tr>
<td>Placebo</td>
<td>B</td>
<td>N2</td>
</tr>
</tbody>
</table>

The estimated risk ratio is given by the equation: \( RR = \frac{a}{N1} / \frac{b}{N2} \).

The logarithm of the relative risk is further computed as 
\[ Y = \log(\text{RiskRatio}) = \ln (RR) \]

The estimated variance of the LogRiskRatio is:
\[ VY = \frac{1}{a} - \frac{1}{N1} + \frac{1}{b} - \frac{1}{N2} \]
The overall effect size is computed as followed:
First a weight \((W)\) is computed for each study. The weight is the inverse of the study’s variance and it is used to compute the overall variance (as shown below): \(W = 1/V\)

The total weight \((W*)\) for each study is the inverse of the total variance \((V*)\). The total variance is the sum of the within studies variance \((V)\) (as shown above) plus the estimate of the between studies variance \((T^2)\). The within studies variance is the variance due to sampling error. The between studies variance is the true variation in the effect sizes due to the different study design. This is the reason for applying a random effect model. If all studies had the same study design and were conducted by the same scientists, the total variance would be equal to the within studies variance and a fixed effect model would have been used.

The between studies variance \((T^2)\) is computed as follows:
\(T^2 = (Q- df)/ C\)
with
\(Q = \sum WiYi^2 - (\sum WiYi/ \sum Wi),\)
\(df\) (degrees of freedom) = \(k-1\) (\(k\) = number of studies), and
\(C = \sum Wi - (\sum Wi^2/ \sum Wi),\) where \(Wi\) is the weight of each study.

The overall effect size is given by the equation:
\(M* = \sum Wi*RR / \sum Wi*\)

The variance \(VM*\) is:
\(VM* = 1/ \sum Wi*\)

The standard error \(SEM*\) is:
\(SEM* = \sqrt{VM*}\)

The 95% lower (LLM*) and upper (ULM*) limits are:
\(LLM* = M* - 1.96* SEM*\)
\(ULM* = M* + 1.96* SEM*\)

The Z-Value for normal cumulative distribution is given by the equation:
\(Z* = M*/ SEM*\)

For a two tailed test the p-value is computed using the equation:
p = 2*(1 - \(\Phi(Z*)\)), where \(\Phi(Z*)\) is the standard normal cumulative distribution.

The heterogeneity (\(F\)):
\(F = (Q- df)/Q *100\%\) (\(Q\) and df defined in §2.2.1.)

The 95% limits are computed as follows:
\(B = 0.5(\ln(Q) - \ln(df))/ (\sqrt{2Q} - \sqrt{(2*df - 1)})\)
\(L= \exp(0.5ln(Q/df) - 1.96*B)\)
\(U= \exp(0.5ln(Q/df) + 1.96*B)\)
Lower Limit: \(LLF^2 = (L^2 - 1)/L^2\) (*
Upper Limit: \(ULF^2 = (U^2 - 1)/ U^2\) (**)

b) Why was the forest plot used?
The forest plot visualizes the overall effect as well as gives a quick impression on the contribution of each single study. This seemed to be of particular importance since at first a high heterogeneity emerged and second may researcher consider it obligatory to include a forest plot in the meta-analysis.

c) If responders/not responders was primary outcome and number of drop outs, the number of patients with adverse effects and the quality of life were the secondary outcomes, what were the predictors of the study?

The meta-analysis includes only studies which compared the antidepressant to a placebo condition. Therefore the treatment condition was the independent variable in all studies entering the analysis. In the subgroup analysis we used the study properties as predictors: inclusion criteria, analysis strategy, cancer stage, and substance group. We clarified this in the revised Results section:

‘The selected predictors were: 1. depression vs. depressive symptoms as eligibility criteria; 2. analysis on an intention-to-treat (ITT) basis vs. completers’ analysis; 3. inclusion of all or only advanced cancer stages vs. inclusion of only early stages; and 4. the substance group SSRI vs. tetracyclic antidepressants (mianserin).’

Page 8, lines 21-24

d) To check the differences between studies, did authors use any homogeneity test? If yes, which one?

The heterogeneity was described in the results. We added a sentence to the methods section:

‘Heterogeneity I² was computed in order to assess the percentage of the overall variability attributed to the between studies variability.’

Page 6, lines 23-24

8. Figures, tables and graphs should be sent as supplement files. But the authors have embedded figures, tables and graphs. So I would request authors to follow the instructions.

Some reviewers seem to prefer a more comprehensive presentation of the manuscript, but in the resubmission we follow the instructions more stringently.

9. The authors describe heterogeneity in the results section, but they fail to mention about it in the methods section. So authors need to make this change.

Done, see question 7d.

10. The findings from the forest plot and the funnel plot should be mentioned seperately from the figures.
Forest plot: In the results section it now reads as:

‘The overall effect size in the analysis is RR=1.56 with 95%-CI: 1.07-2.28 (p= 0.021), i.e. under the antidepressants a therapeutic response (as defined in the considered studies) is about 50% more likely than in the placebo group (see Table 2 and forest plot in Figure 1). Four studies found a positive effect of the antidepressants on depressed cancer patients. In the other two studies no significant difference emerged but the 95% confidence intervals were wider than those of the four other studies (Figure 2)”

Page 8, lines 2-7
Funnel plot: In the results section it now reads as:
‘Finally, no indication for a publication bias can be derived from the funnel plot; in particular small
studies seem not to have higher effect sizes than larger trials (Figure 4).’

**Page 9, lines 21-23**

**11. The writing needs to be more cohesive and flowing smoothly from one topic to another.**
We revised the ms throughoutly and particularly shortened parts which addressed topics that were not strictly related to the aim of the meta-analysis.

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1 David Taylor, Nicholas Meader, Victoria Bird, Steve Pilling, Francis Creed and David Goldberg
Chronic physical health problems: systematic review and meta-analyses of safety and efficacy
BJP 2011, 198:179-188.