

05-Nov-2023

BMJ-2023-078084 entitled "The efficacy of psilocybin for the treatment of depressive symptoms: a systematic review and meta-analysis"

Dear Ms. Metaxa,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Associate Editor
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****Report from The BMJ's manuscript committee meeting****

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder, (chair) Tim Cole (statistical editor), Nazrul Islam, Tim Feeney, Tiago Villanueva, Alexander Mafi, Juan Franco, John Fletcher, Emma Rourke (BMJ Medicine)

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- We were wondering whether you would be interested in making this a living systematic review.
- It's a very dense and crowded paper and the paper needs to be made much more readable.
- We were concerned that the gaps in the literature were not clearly identified and that the findings are similar to other systematic reviews.
- It's not clear what Hedge's g is, something more transparent would be preferable
- Should use baseline-adjusted change in outcome rather than simple change.
- Please define direction of rating scales.
- Methods appear in Results.
- It was not clear what the finding was really- so you say, "The meta-analysis showed a significant benefit for psilocybin (Hedge's $g=1.64$, 95%CI: 0.55 to 2.73, $p<0.001$)..." and then you say "...in favor of placebo" for the main outcome. Please clarify.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

Thanks for inviting me to review such an interesting paper.

The manuscript is very well written.

The literature reviewed is updated, and as far as I know, the trial has been conducted according to the standards for this kind of analysis.

This method and results parts are clear, however some part of the manuscript might need to be slightly revised.

Please find below some comments for different parts of the manuscript.

Abstract- Clear

Keywords- Clear

COI: clear

Intro: well written, informative.

Comment 1- Introduction p.4

Current evidence on psilocybin's effectiveness for depressive symptoms.

Authors do not really discuss the dose of psilocybin (10.1016/j.euroneuro.2023.07.011), It would be valuable to consider incorporating information related to the optimal dosage and its relevance to specific patient subgroups. This could be included in either the introduction or the discussion section of the paper to provide a more comprehensive understanding of the study's implications

Methodology- very clear

Comment 2-

Was the study's methodology inclusive of control groups utilizing psychotherapy, and were antidepressants considered within the control condition, which could encompass non-active comparators like placebo, niacin, or psychedelic microdosing, as mentioned?

Comment 3- Authors should be aware that psilocybin can have an effect, starting at doses as low as 3mg/70kg

“ Studies where the active psilocybin condition involves micro dosing (i.e., psilocybin below 100 µg/kg) were excluded.”

Comment 4- Search Strategy

Were articles screened independently by two different authors?

Comment 5

“Subgroup analysis” “ Number of doses and amount of psilocybin administered”

The authors should exercise caution in distinguishing between a psychedelic-naïve population and participants who may have had prior experiences with psilocybin more than a year before being enrolled in trials. It's crucial to acknowledge that the antidepressant effects of psilocybin are reported to endure for at least six months but tend to wane after a year. This differentiation and recognition of the temporal aspects are crucial for a more accurate interpretation of the study's outcomes.

Comment 6

“ Reasons for exclusion”> I suggest that this part could go to the supplements

Comment 7

Table: How do authors define psychological support?

The authors should consider a comprehensive discussion of this point in the paper's discussion section. It is challenging to assess the potential influence of prior experiences with psychotherapy, psychological support, or active shamanic sessions on the patients included in the study. Exploring this aspect in the discussion would provide valuable insights into the nuanced factors that may affect the outcomes and interpretations of the research.

Comment 8

“ Side effects and adverse events observed across studies”

There is one trial where a patient had vivid dreams and insomnia lasting more than 24 hours and required medication and maybe one case of some thought disturbance if I remember. Check (10.1016/j.euroneuro.2023.07.011). Bipolar/schizophrenia patients might be more susceptible to such adverse events.

More largely side-effects are reported with different scales and methods in each trials...

Comment 9- “ The percentage of participants with prior psychedelics use may have a significant effect on depression score changes ($p=0.002$),” This is an important finding that should be highlighted.

Additional Questions:

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Reviewer: 2

Recommendation:

Comments:

Thank you for the opportunity to review this manuscript. The authors conducted a meta-analysis of randomized trials testing psilocybin for depression vs. placebo or non-psychoactive pharmacological agent. They founded evidence that psilocybin reduces depression symptoms over placebo, although evidence certainty was low due to heterogeneity and risk of small study bias. They found some evidence for moderators of this effect.

I think this study has several strengths. It was well written and easy to follow. The risk of bias assessment and GRADE evaluation were helpful as was the evaluation of response and remission rates. It was preregistered through PROSPERO. It addresses a timely topic. These strengths aside, I have some questions about the study and its reporting that I think are worth considering. I hope the authors and editor find these helpful.

1. The primary question / concern that arose for me is whether this study adds information that moves substantially beyond other meta-analyses that have been published on this topic, including a recent meta-analysis focusing specifically on psilocybin for depression (Haikazian et al., 2023, Psychiatry Research). Indeed, it appears that the Haikazian et al. meta-analysis actually includes a trial that I believe would be eligible for inclusion in the current meta-analysis but was not included I'm guessing because it appeared after the current study's search was completed (Raison et al., 2023, JAMA). The current meta-analysis provides GRADE assessment and tests some moderators not explored in the Haikazian et al. paper. Whether the current meta-analysis is sufficiently novel to warrant publication in BMJ is, of course, an editorial decision.

2. I appreciated the authors preregistering their study in PROSPERO. However, it appeared to me that the preregistration as reported in supplemental materials was slightly different from that on the PROSPERO website. For example, the subgroup analysis in the manuscript is not entirely consistent with the "analysis of subgroups or subsets" section on the PROSPERO record.

3. I was curious how the authors determined whether there were sufficient studies to conduct meta-regression. I may have missed it, but I did not see this specified in the preregistration.

4. I was curious if the authors managed to obtain results from studies that were completed but not yet published. It would be helpful to more clearly report how many such studies existed.

5. It was not clear to me why the authors reviewed some secondary outcomes (e.g., White Bear Suppression Inventory) that were not depression specific.

6. I think it is reasonable to include the studies that looked at depression in the context of terminal cancer (although I think one could also argue that end-of-life depression is distinct from typical depression / MDD). However, I wondered to what extent tests of moderation were confounded with there being much larger effects for these trials (e.g., $d = 4.52$ in Griffiths et al., 2016). For example, were the end-of-life samples also older?

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