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# Treating Bipolar Depression Using Psilocybin-Validity Threats Regarding Efficacy and Safety

Eiko Fried, Ioana Cristea, Florian Naudet

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Letter to the editor, 400 words, 5 references

**“Treating bipolar depression using psilocybin: validity threats regarding efficacy and safety”**

Dr. E. I. Fried, Department of Psychology, Clinical Psychology Unit, Leiden University;  
[eiko.fried@gmail.com](mailto:eiko.fried@gmail.com) (corresponding author)

Dr. Ioana A. Cristea, Department of General Psychology, University of Padova, Italy,  
[ioanaa.cristea@unipd.it](mailto:ioanaa.cristea@unipd.it)

Prof. F. Naudet, University of Rennes, CHU Rennes, Inserm, Irset (Institut de recherche en santé, environnement et travail)  
[floriannaudet@gmail.com](mailto:floriannaudet@gmail.com)

According to the study protocol, the recently published n=15 study by Aaronson et al.<sup>1</sup> was carried out “to assess safety and efficacy [...] of 25 mg of psilocybin in patients with treatment-resistant type 2 bipolar depression”. We see three concerns.

First, the study title “non-randomized controlled trial” is incorrect and misleading because there is no control group. Consistent with the authors’ description as “uncontrolled, open-label study” (p. E7), we ask the journal to issue a correction.

Second, the trial deviates from the most recent criteria for defining treatment-resistant bipolar depression (TRBD) requiring  $\geq 8$  weeks of treatment with a prespecified set of pharmacological agents<sup>2</sup>. These criteria, cited in the introduction yet not used in defining patient eligibility, incorporate updates in treatment guidelines regarding the differences in efficacy between treatments. Because previous pharmacological treatments are not described in the paper, it is unclear how many patients fit these more stringent TRBD criteria.

Third, we were surprised to see the Journal publish a study with a design that does not allow to answer the authors’ research questions about efficacy and safety. To understand whether psilocybin explains part of the strong observed pre-post change ( $d=4.08$ ), a control group is crucial. As is, the design can account neither for non-specific (including placebo) effects nor regression to the mean. Lack of blinding increases expectancy effects in patients, and can bias researchers, interviewers, and data analysts who know the desired results. Moreover, all participants received psychotherapy, and some additional pharmacotherapy, likely contributing to the observed pre-post changes. Further, many approached participants were deemed ineligible due to psychiatric complications such as comorbidity, likely increasing responsiveness to treatment in the enrolled 15 patients compared to normal psychiatric settings in which comorbidities are commonplace. Finally, we could not find the authors’ rationale for reporting on some (e.g., PHQ-9) but not other (e.g., GAD-7) secondary outcomes. Such transparency is particularly relevant given that the study is industry-sponsored and several authors declare conflicts of interest, both of which are related to more favorable study outcomes<sup>3,4</sup>. Overall, these challenges also impact inferences regarding safety: a small, highly selected sample in an open label study cannot establish whether a treatment should be considered safe. If severe adverse events occurred in 10% of participants, many n=15 studies would miss these.

In the future, we recommend editors and reviewers use the recently developed checklist to assess validity threats in psychedelic science, which reveals the issues listed above<sup>5</sup>.

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## **Conflicts of interests**

EIF & IAC have no conflicts of interests related to the topic of the present manuscript.

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