come trends absent exposure) having the same rate of change for the comparison group (for the SCM, the synthetic control group) and treatment group.

Importantly, although SCM achieves parallel trends during the preintervention period, this does not imply parallel trends for the full study period because of possible regression to the mean.[2-4] Specifically, if outcome trends of donor units reflect higher-than-average or lower-than-average trends of the full comparison group, then outcome trends of donor units will tend to revert back to the mean trend of the comparison group after matching is no longer enforced, ie, during the postintervention period.

In the scenario considered here, the level of fatal overdoses in all comparison units is greater than the level of fatal overdoses in Oregon (Figure 2).[1] Thus, regression to the mean bias would imply that donor units would revert back to a greater mean during the postintervention period, resulting in a negative bias. The SCM could even be more biased than difference in differences if the parallel trends assumption is indeed met.

Researchers should be critically aware of assumptions and limitations of the methods they use. Understanding and investigating such assumptions is the cornerstone of rigorous quasiexperimental research that establishes credible estimates of policy changes.

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Editorial Note: This letter was shown to the corresponding author of the original article, who declined to reply on behalf of the authors.

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Treating Bipolar Depression Using Psilocybin—Validity Threats Regarding Efficacy and Safety

To the Editor According to the study protocol, the recently published study by Aaronson et al[1] was carried out "to assess effectiveness of 25 mg of psilocybin in [15] patients with treatment-resistant type 2 bipolar depression." We see 3 concerns.

First, titling the study a nonrandomized controlled trial is incorrect and misleading because there is no control group. Consistent with the authors' description as "uncontrolled, open-label study,"[1] we ask the journal to issue a correction.

Second, the trial deviates from the most recent criteria for defining treatment-resistant bipolar depression requiring 8 or more weeks of treatment with a prespecified set of pharmacological agents.[2] 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 article, is it unclear how many patients fit these more stringent treatment-resistant bipolar depression criteria.

Third, we were surprised to see the journal publish a study with a design that does not allow the authors to answer their research questions about efficacy and safety. To understand whether psilocybin explains part of the change in Montgomery-Åsberg Depression Rating scale score observed from before to after treatment (Cohen d = 4.08), a control group is crucial. As is, the design can account neither for nonspecific (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 changes observed from before to after treatment. Further, many approached participants were deemed ineligible due to psychiatric complications, such as comorbidities, 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 (eg, Patient Health Questionnaire-9) but not other (eg, General Anxiety Disorder-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.[3,4] 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 studies with 15 participants would miss these.

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

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1. Aaronson ST, van der Vaart A, Miller T, et al. Single-dose synthetic psilocybin with psychotherapy for treatment-resistant bipolar type II major depressive episodes: a nonrandomized controlled trial. *JAMA Psychiatry*. Published online December 6, 2023. doi:10.1001/jamapsychiatry.2023.4685

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In Reply We thank Fried et al for their thoughtful remarks about our article.[1] The first issue they raised concerned the description of our study as a nonrandomized controlled trial. This could be problematic, as there was no comparator group or other control for non-specific effects. However, the nature of the study design was clearly described in the article and the accompanying editorial, which stated, "Aaronson and colleagues present an important step forward in this single-arm open-label study of psilocybin in patients with bipolar II depression."[2] We elected to use the phrase "controlled trial" to reflect the stringency of participant selection and the prohibitions on other psychotropic drugs before and after psilocybin dosing. However, to avoid confusion, we agree to amend the subtitle to a nonrandomized open-label trial.[3]

The second concern was that our study did not evaluate resistance to prior antidepressant treatments based on the criteria proposed in a recent expert opinion article.[4] Instead, we evaluated treatment-resistance with the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire,[5] a widely used and validated instrument that evaluates resistance to a broad range of antidepressant medications. The consensus opinion article offered a narrow definition of treatment resistance, as the medications considered were limited to 3 mood stabilizers and 3 atypical antipsychotics. While we only required 2 failed adequate trials for study inclusion, our mean (SD) number of adequate failed trials was 4.27 (1.5), and all adequate trials had a minimum duration of 8 weeks.

The third criticism was the most concerning, as the argument was offered that there is little to be learned from open-label trials of a novel compound in a novel illness target. We reported on the first clinical experience of the use of a psychedelic in patients with treatment-resistant bipolar II in a major depressive episode, a common condition with a dire clinical need for new safe and effective interventions. We emphasized that, while the findings were encouraging, the sample size and open-label design tempered conclusions about safety and efficacy. However, had we observed a high rate of adverse effects, such as switches to hypomania or mania, or ineffectiveness, there would be reduced interest in investing in a rigorous randomized and blinded controlled trial. As noted in the accompanying editorial, our study "deserves a controlled follow-up,"[2] perhaps including some of the methodological features Fried et al found lacking in our report.

Development of novel treatments requires open-label trials that set the stage for more rigorous research. We share the concerns of Fried et al and the editorial that psychedelic research elicits both unjustified enthusiasm and antagonism. Psychedelic research brings special challenges regarding participant blinding and the complication of psychotherapeutic support. However, the observation in this study that 12 of 15 patients with treatment-resistant bipolar depression maintained remission 3 months after a single dose of psilocybin dosing seems worthy of both report and future investigation.

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1. Aaronson ST, van der Vaart A, Miller T, et al. Single-dose synthetic psilocybin with psychotherapy for treatment-resistant bipolar type II major depressive episodes: a nonrandomized controlled trial. *JAMA Psychiatry*. Published online December 6, 2023. doi:10.1001/jamapsychiatry.2023.4685

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CORRECTION

Error in Title and Text: The Original Investigation titled "Single-Dose Synthetic Psilocybin With Psychotherapy for Treatment-Resistant Bipolar Type II Major Depressive Episodes: A Nonrandomized Open-Label Trial,"[1] published on December 6, 2023, was corrected to revise the study type in the title and text from "a nonrandomized controlled trial" to "a nonrandomized open-label trial." This article was corrected online.

1. Aaronson ST, van der Vaart A, Miller T, et al. Single-dose synthetic psilocybin with psychotherapy for treatment-resistant bipolar type II major depressive episodes: a nonrandomized open-label trial. *JAMA Psychiatry*. Published online December 6, 2023. doi:10.1001/jamapsychiatry.2023.4685