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Viewpoint

On blinding and suicide risk in a recent trial of psilocybin-assisted therapy for treatment-resistant depression

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Results from a recent Phase II trial of psilocybin-assisted therapy for treatment-resistant depression[1] suggest modest efficacy but raise concerns about potential for serious adverse effects. The study highlights the need for rigorous assessment of blinding integrity, expectancy, and further study of factors that may contribute to risk in vulnerable populations.

Progress in clinical psychedelic research was recently punctuated by publication of results from a multi-site study testing the efficacy and safety of psilocybin for treatment-resistant depression (TRD).[1] Though the results from Goodwin et al.[1] may be interpreted as promising, the study was unfortunately a missed opportunity to gain clarity on problems that have plagued research in this area to date, and also raised concerns regarding safety. A total of 233 participants across 22 sites throughout Europe and North America were randomized to receive a single dose of either 25, 10, or 1 mg of a proprietary formulation of psilocybin, with the latter dose functioning as a placebo condition. Participants were required to have failed 2–4 medication trials in the current depressive episode to qualify. The authors reported that the 25 mg but not 10 mg dose was significantly more effective at reducing depressive symptoms than 1 mg at 3 weeks. Key secondary endpoints including rates of treatment response and remission at 3 weeks and sustained response at 12 weeks were determined to not be significantly different across doses.

While the 37% response rate at 3 weeks in the high-dose group was lower than in previous studies of psilocybin-assisted therapy for depression,[2,3] several points are important to contextualize this result. As the authors highlighted, this was a treatment-resistant sample, and the rate of treatment response was numerically higher than response rates for second, third, and fourth line treatments in STAR*D (30.6%, 13.7%, and 13.0%, respectively).[4] Further, antidepressant effects were evident as soon as 1 day after treatment. Additionally, recent research has raised concern about the potential of antecedent antidepressant use to dampen response to psilocybin and related drugs.[5] Yet despite 67% of the sample being tapered off an antidepressant at study entry, the 25 mg treatment group still had significant reductions in depression severity relative to the 1 mg group at three weeks. Finally, the study design used by Goodwin et al.[1] had fewer doses and incorporated less psychotherapeutic support compared to the two previous smaller open-label studies in depressed patients that reported higher efficacy.[2,3] Whether repeated doses might have additive therapeutic effects remains an open and important clinical question.

Perhaps the most glaring criticism of this work is on the issue of blinding. As is widely acknowledged, the subjective effects of classic psychedelics are usually obvious enough to allow both participants and study staff to correctly guess treatment allocation in placebo-controlled trials.[6] This was reconfirmed in a recent trial comparing psilocybin with diphenhydramine in patients with alcohol use disorder, in which 94% and 92% of participants and staff respectively correctly identified their treatment condition after the first dose.[7] The medium dose (10 mg) condition in Goodwin et al.[1] could have provided novel insights on the role of expectancy if it was determined to be a convincing comparison condition with the high dose. Unfortunately, the authors failed to collect any data on blinding integrity. Given the ubiquitous concern about this issue and the ease with which this data could have been collected, its omission seems remarkable and highlights the need for more publicly funded clinical trials. Of note, less than two weeks after these results were published, National Institute of Mental Health (NIMH) released a Notice of Information indicating that clinical trials using psychedelics without rigorous assessment of blinding integrity would be considered of low funding priority.[8]

Another point of concern is the relatively high rate of adverse events, which included suicidal behavior among three participants. These occurred between about one to two months after treatment. All three were noted to be non-responders at three weeks and had previous suicide attempts or non-suicidal self-injurious behavior. While history of prior attempts confers a higher risk, and patients with TRD may generally be expected to have elevated risk, all suicidal behavior in this trial occurred

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in the high-dose treatment arm and should be considered seriously. Increased suicide risk with serotonergic antidepressant drugs has been a concern since at least the 1960s, though the mechanism by which this occurs (typically in younger people early on in treatment) remains unclear.[9] A few commonly espoused theories include progression of depression, antidepressant-induced "activation syndrome", and precipitated shifts into other mood states including mixed and manic states. Existing research on the underlying neurobiological mechanisms of these phenomena may shed light on potential mechanisms of increased suicide risk with psychedelics. Of similar importance would be the prospective collection of detailed data on timing and onset of worsening suicidal ideation and potentially related symptoms such as insomnia, anxiety, and irritability.

While turning to the existing literature on suicide risk with common classes of antidepressants may be a helpful place to start, additional mechanisms unique to psychedelics should also be considered. One possibility in the current cultural milieu is that of a demoralization reaction. With recent media portrayals of psychedelics as cure-all drugs,[10] patients who have failed to find relief from other treatments may come to see psychedelics as a last resort. If a study participant believes they have received a much-hyped treatment and still fails to see improvement, demoralization and hopelessness may ensue. It is also worth noting that optimizing aftercare (e.g., type, timing, frequency) in psilocybin-assisted treatment may be important to mitigating serious risks in vulnerable populations. The present study had less support relative to existing trials such as Davis et al.,[2] which had about 11 h of supportive psychotherapy between preparation and one month follow-up. Lastly, challenging psychedelic experiences and their sequelae also deserve further attention as potential contributors to risk.

Overall, Goodwin et al.[1] present an important step forward in our understanding of real-world risks and benefits associated with the use of classic psychedelics in clinical populations. Attention to issues of blinding integrity and development of adequate comparison conditions will be key for future studies. The risk of serious adverse events such as suicide ought to be carefully studied and may have contributing factors that are unique to this treatment.

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