Psychedelic Therapies: One Drug, Multiple Treatments

Reply to Modesto-Lowe et al

To the Editor: We appreciate the thoughtful letter to the editor by Modesto-Lowe et al[1] regarding the contribution of psychosocial interventions to psychedelic drug treatments. As they emphasized, the context of drug administration is widely believed to influence the psychological effects of classical psychedelic drugs, which have been characterized as nonspecific amplifiers of consciousness[2] and meaning-response magnifiers.[3] There is substantive neurophysiologic evidence that suggests this psychological property may be mediated through serotonergic receptor modulation of the dopamine release.[4] Thus, providers' beliefs about these compounds could impact patients due to variation in study protocols and provider behaviors, which may in turn affect treatment efficacy.[5] Neuromodulatory approaches to psychedelic treatments—which emphasize pharmacological drug effects as the primary therapeutic mechanism—may carry different risk-benefit profiles relative to emotive approaches,[6] such as integration within group psychotherapy.

Although there is substantial evidence supporting a key role for set and setting in influencing the effects of classical psychedelic drugs,[5] there is not high-quality evidence that clearly demonstrates the superiority of specific psychological support approaches for particular psychiatric conditions. Historically, prominent 20th century researchers from the Spring Grove Hospital Center felt strongly about the importance of intensive preparatory psychotherapy and settings intended to promote mystical experiences in the clinical use of lysergic acid diethylamide (LSD),[2,7,8] and many current researchers also emphasize the importance of psychotherapy to treatment outcomes.[9–13] Clinically significant 20th century research results suggested that superior outcomes were achieved in the treatment of alcohol use disorder (AUD) with LSD through psychotherapy-intensive methods employed at Spring Grove,[7,8,14,15] a pattern in many ways consistent with recent results of psilocybin trials for AUD.[16,17] However, randomized controlled trials have not established the superiority of specific psychological support approaches for any disorder. Factorial studies conducted in the treatment of AUD with LSD during the 20th century had significant design limitations,[7,18–20] and no such studies have been published in the 21st century. Psychotherapy itself is an intervention that carries its own complexities and unique risks, which may be amplified in the setting of psychedelic drug administration.[21,22]

In their letter, Modesto-Lowe et al[1] discuss the potential of group settings for psychedelic treatments. The perceived effectiveness of integrating psychedelics within group settings was among the most agreed upon survey items for our respondents[6] despite the fact that the research supporting this approach is limited.[23] This common belief might be explained by the fact that historically, various cultures with approved uses of psychedelic plants or fungi have taken them in ceremonial group settings,[24,25] and they continue to be used in these settings today.[26] Group administration of high-dose psychedelics has previously been considered challenging by researchers, in part due to difficulties in maintaining group cohesion during peak drug effects.[2] Recent research applying this model has most often used individual dosing combined with group psychotherapy pursued outside of peak drug effects,[27,28] though other practitioners have pursued group administration in clinical settings.[29] Group approaches may offer distinct benefits, such as making treatment more accessible and harnessing group support to improve the quality of the experience. However, group approaches will likely carry their own unique complexities and risks.

Several pharmaceutical companies advancing psychedelic treatments have emphasized their use of drug-focused models which minimize the role of psychotherapy,[30–32] decisions that likely relate in part to the goal of expeditious regulatory approval. However, such approaches may not be optimal methods for implementing psychedelic compounds as psychiatric treatments, and the data generated from these studies should not be fully extrapolated to represent the safety and efficacy of psychedelic drugs administered with more extensive psychological support models. Investigator-initiated research and public funding will be key to enable the evidence-based expansion of psychedelic treatments alongside a variety of psychological support models.

References

1. Modesto-Lowe V, Sgambato D, Chaplin M. Toward consensus in psychedelic-assisted therapy: the critical role of psychotherapeutic support. *J Clin Psychiatry*. 2025;86(3):25lr15978.
2. Grof S. *LSD Psychotherapy*. 2nd ed. Hunter House; 1994.
3. Hartogsohn I. *American Trip: Set, Setting, and the Psychedelic Experience in the Twentieth Century*. The MIT Press; 2020.
4. David A, Bender JSS. Psychedelic psychiatry. In: Fuerhlein MGB, ed. *Encyclopedia of the Neurological Sciences*. Academic Press; 2025:670–685.
5. Carhart-Harris RL, Roseman L, Haijen E, et al. Psychedelics and the essential importance of context. *J Psychopharmacol*. 2018;32(7):725–731.
6. Bender DA, Nayak SM, Siegel JS, et al. Psychological support approaches in psychedelic therapy: results from a survey of psychedelic practitioners. *J Clin Psychiatry*. 2025;86(1):24m15521.
7. Oram M. *The Trials of Psychedelic Therapy: LSD Psychotherapy in America*. Johns Hopkins University Press; 2018.:ix.
8. Pahnke WN, Kurland AA, Unger S, et al. The experimental use of psychedelic (LSD) psychotherapy. *JAMA*. 1970;212(11):1856–1863.

9. Bogenschutz MP. Pharmacological and nonpharmacological components of psychedelic treatments: the whole is not the sum of the parts. *Am J Psychiatry*. 2024;181(1):75.
10. Alpert MD, O'Donnell KC, Paleos CA, et al. Psychotherapy in psychedelic treatment: safe, evidence-based, and necessary. *Am J Psychiatry*. 2024;181(1):76–77.
11. Earleywine M, De Leo J, Bhayana D, et al. Psilocybin without psychotherapy: a cart without a horse? *Am J Psychiatry*. 2024;181(1):78–79.
12. O'Donnell KC, Anderson BT, Barrett FS, et al. Misinterpretations and omissions: a critical response to Goodwin and colleagues' commentary on psilocybin-assisted therapy. *Am J Psychiatry*. 2024; 181(1):74–75.
13. Schenberg EE, King F, 4th, da Fonseca JE, et al. Is poorly assisted psilocybin treatment an increasing risk? *Am J Psychiatry*. 2024;181(1):75–76.
14. Pahnke WN, Kurland AA, Unger S, et al. The experimental use of psychedelic (LSD) psychotherapy. *Int Z Klin Pharmakol Ther Toxikol*. 1971;4(4): 446–454.
15. Kurland A, Savage C, Pahnke WN, et al. LSD in the Treatment of Alcoholics. Presented at the 7th International Congress, CINP; August 11–15, 1970; Prague, Czechoslovakia.
16. Rieser NM, Bitar R, Halm S, et al. Psilocybin-assisted therapy for relapse prevention in alcohol use disorder: a phase 2 randomized clinical trial. *eClinicalMedicine*. 2025;82:103149.
17. Bogenschutz MP, Ross S, Bhatt S, et al. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry*. 2022;79(10):953–962.
18. Ludwig A, Levine J, Stark L, et al. A clinical study of LSD treatment in alcoholism. *Am J Psychiatry*. 1969; 126(1):59–69.
19. Ludwig AM, Levine J. A controlled comparison of five brief treatment techniques employing LSD, hypnosis, and psychotherapy. *Am J Psychother*. 1965;19: 417–435.
20. Johnson FG. LSD in the treatment of alcoholism. *Am J Psychiatry*. 1969;126(4):481–487.
21. Goodwin GM, Malievskaia E, Fonzo GA, et al. Must psilocybin always "assist psychotherapy"? *Am J Psychiatry*. 2024;181(1):20–25.
22. Anderson BT, Danforth AL, Grob CS. Psychedelic medicine: safety and ethical concerns. *Lancet Psychiatry*. 2020;7(10):829–830.
23. Trope A, Anderson BT, Hooker AR, et al. Psychedelic-assisted group therapy: a systematic review. *J Psychoactive Drugs*. 2019;51(2):174–188.
24. Fernandez JW. *Bwiti: An Ethnography of the Religious Imagination in Africa*. Princeton University Press; 1982.
25. Myerhoff BG. *Peyote Hunt: The Sacred Journey of the Huichol Indians.* In book series: *Symbol, Myth, and Ritual*. Cornell University Press; 1974.
26. Hartogsohn I. Set and setting in the Santo Daime. *Front Pharmacol*. 2021;12:651037.
27. Anderson BT, Danforth A, Daroff PR, et al. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: an open-label safety and feasibility pilot study. *eClinicalMedicine*. 2020;27: 100538.
28. Agrawal M, Richards W, Beaussant Y, et al. Psilocybin-assisted group therapy in patients with cancer diagnosed with a major depressive disorder. *Cancer*. 2024;130(7):1137–1146.
29. Oehen P, Gasser P. Using a MDMA- and LSD-Group therapy model in clinical practice in Switzerland and highlighting the treatment of trauma-related disorders. *Front Psychiatry*. 2022;13:863552.
30. Hardman J. MindMed's 'Total Elimination' of Psychotherapy in LSD Study Stokes Debate Around Its Role in Psychedelic Therapies. *Psychedelic Alpha*. April 5, 2024. https://psychedelicalpha.com/news/mindmeds-total-elimination-of-psychotherapy-in-lsd-study-stokes-debate-around-its-role-in-psychedelic-therapies. Accessed July 11, 2025.
31. Hardman J. Compass Pathways CEO Kabir Nath Discusses Commercialisation, "Psychological Support" and Competitive Landscape. Psychedelic Alpha; 2024. https://psychedelicalpha.com/news/interview-compass-pathways-ceo-kabir-nath-discusses-commercialisation-psychological-support-and-competitive-landscape. Accessed July 11, 2025.
32. Pollack M, Hocevar-Trnka J, Taylor B, et al. RE104: A Novel Serotonergic Psychedelic 4-OH-DiPT Prodrug. Presented at the American Society of Clinical Psychopharmacology Annual Meeting; May 27–30, 2025; Scottsdale, Arizona. https://reunionneuro.com/wp-content/uploads/2025/05/25-RNR-5038_ASCP24_RE104_Encore_L2-2.pdf

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