

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 al¹ 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 consciousness² 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 al¹ 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 respondents⁶ 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.

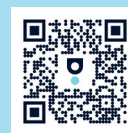
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