Critique/commentary

Out of control: Blinding, dose response, and psychosocial controls in psychedelic trials

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Abstract

As psychedelic clinical trials expand in scale and influence, foundational challenges in trial design have come into sharper focus. In this commentary, we examine three interrelated issues: 1) the failure of blinding in psychedelic trials, 2) the potential of alternate controls including dose–response designs as an empirical workaround, and 3) the persistent ambiguity surrounding psychosocial control conditions. We argue that efforts to preserve traditional placebo-controlled frameworks are often inadequate due to the unmistakable subjective effects of psychedelics and the therapeutic relevance of those effects themselves. Instead, we highlight alternative designs including graded dose comparisons and unblinded comparative efficacy studies as pragmatic paths forward. Finally, we outline a proposal for empirically isolating the role of psychotherapy in psychedelic treatment, emphasizing the need for operational definitions, fidelity monitoring, and careful risk mitigation. These issues are unlikely to be resolved by any single design; rather, progress will require triangulating evidence across multiple imperfect but complementary methodologies.

Keywords

study design, psychedelic science, blinding, study controls

Blinded, randomized controls in drug trials are intended to isolate the active ingredient of a therapeutic intervention from extraneous factors that may cause improvement, such as spontaneous remission, regression to the mean, and placebo effects—including patient expectancies. Blinding also serves to restrain allegiance effects on the part of therapists and researchers. Blinding is thus vitally important to the integrity of these controls; when it fails, expectancy effects can be unleashed which influence treatment outcomes.

The vast majority of clinical drug trials (90%) fail to clear their primary endpoint, often through failure of the drug treatment to differentiate from placebo (Sun et al., 2022). Uniquely however, a new drug application of 3,4-methylenedioxymethamphetamine (MDMA) for post-traumatic stress disorder (PTSD) was rejected even though it nominally met its safety and efficacy endpoints. The Psychopharmacologic Drugs Advisory Committee voted nearly unanimously "that the data did not show that midomafetamine (MDMA) was effective in patients with PTSD. Many stated that the functional unblinding, the lack of management of expectation bias and selection bias limited the interpretability of the efficacy analyses" (FDA, 2024a). While the Food and Drug Administration's (FDA) own reasons for rejecting MDMA quite likely differ from those of the Advisory Committee, blinding and the quality of the control condition clearly loomed large in the surrounding discussion.

In psychedelic trials, blinding is extremely challenging due to the profound and obvious subjective effects which render it nearly impossible. While unblinding is certainly a shared problem among other psychiatric drug trials, it may be a greater challenge in psychedelic research due to heightened expectations and hype surrounding psychedelic effects.

When measured, it is clear that by even the most liberal standard, efforts to blind psychedelic trials have roundly failed; upward of 85% of participants can correctly identify a classic psychedelic (Nayak et al., 2023). This includes attempts with active controls such as stimulants, niacin, and dissociatives. Another challenge is that the subjective effects are probably themselves therapeutic (Yaden and Griffiths, 2021). If a control condition perfectly recapitulates the subjective effects of a treatment, and the subjective effects of the treatment are therapeutic, then the control is a treatment.

Unlike with classic psychedelics, MDMA has actually been successfully blinded. In one study, 11 experienced users of both drugs, received either 100 mg MDMA, 20 mg methamphetamine, or 40 mg methamphetamine (Kirkpatrick et al., 2012). Half misidentified 20 mg methamphetamine as MDMA, and MDMA was similarly only correctly identified half the time. This effect was dose-dependent, as 40 mg methamphetamine was mostly identified as methamphetamine. Similarly in a study examining the empathogenic effects of MDMA, 6 out of 21 participants had mistakenly indicated that they had been given MDMA when, in fact, they were given methamphetamine (Bedi et al., 2010). Another study found that methamphetamine produced similar pro-social effects as MDMA, suggesting an overlap in subjective effects (Molla et al., 2023). Importantly, amphetamine does not appear to effectively blind MDMA (Holze et al., 2020). Taken together these findings suggest that methamphetamine may successfully blind MDMA (as one study will attempt (NCT05783817)).

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It may be premature to completely abandon hope for blinding classic psychedelics. It is possible, perhaps likely, that psychedelic-naïve participants, or those less exposed to psychedelic media or hype might achieve better blinding when paired with an active placebo. Psychedelic hype is after all, not universal. The average American continues to view psychedelic use as risky, and this is heightened for certain racial groups, such as African Americans (Barnett et al., 2024). Countries around the world will vary significantly in prevalence of psychedelic use, cultural attitudes toward their use, and in the quality of media exposure, making international, multi-site studies spanning Anglophone and non-Anglophone regions an especially valuable avenue of pursuit.

Still, it seems unlikely that even such measures would adequately blind a placebo. However, there is a far simpler path, likely the least worst solution: using a range of doses and demonstrating a dose response.

The best example of this was Compass's phase 2 study of psilocybin in Treatment Resistant Depression (TRD), testing 1, 10, and 25 mg of psilocybin (Goodwin et al., 2023). The high dose produced significant improvement relative to the low-dose, a 6.6 point drop Montgomery-Asberg Depression Rating Scale (MADRS) scores, while the intermediate dose produced intermediate results, a 2.5-point score drop. In that trial, Oceanic Boundlessness, which correlates so strongly as to be effectively identical to the Mystical Experience Questionnaire (Liechti et al., 2017), predicted depression improvement. Notably, there was substantial overlap in the subjective effects across doses, and the correlation between depression improvement and Oceanic Boundlessness was the same across all three doses ($r = 0.5$; Goodwin et al., 2025). Such a dose–response design may preserve blinding. While such a design is acceptable to the FDA for drug approval, it is not clear they will be acceptable to other regulatory agencies. Despite this, results from this trial were used in support of the break-through designation status application submitted to the FDA.

In a recent development, COMPASS Pathways has released results from its Phase 3 COMP005 trial assessing the effects of a single 25 mg dose of psilocybin in 258 patients with TRD. At the 6-week end-point, they reported a 3.6-point difference in MADRS scores relative to the placebo group (Compass Pathways, 2025). This effect is notably less than that of the phase 2 trials, a common phenomenon in drug trials across several disciplines (Schuhmacher et al., 2025; Vreman et al., 2020). However, it is greater than the Minimal Clinically Important Difference for the MADRS (Duru and Fantino, 2008), and comparable to phase 3 trials of esketamine in the treatment of TRD, which showed MADRS score drops of 3–4 points (Fedgchin et al., 2019; Popova et al., 2019; Ochs-Ross et al., 2020). COMPASS is currently conducting another phase 3 dose response trial that will add to the body of literature regarding drug efficacy and possibly improve blinding.

Unblinding might be a relative problem. During the Advisory Committee for MDMA, the director of FDA's Division of Psychiatry indicated "It may still be possible for a study that is partially functionally unblinded to be considered an adequate and well controlled study if there are adequate methods to minimize bias. . . particularly if the results do not appear to be consistent with what is known about the natural history of the condition" (FDA, 2024b).

There also remains great value to trials that are unblinded by design. Under certain conditions, meaningful causal inferences can still be drawn. Comparative efficacy trials, pitting a psychedelic against an existing effective treatment, can be informative even if unblinded. This is especially the case when spontaneous remission and placebo response are low, the outcome is biologically verifiable, and long-term follow-up is included. For example, an unblinded trial of psilocybin versus nicotine replacement (NCT01943994) would be highly informative if the outcomes are positive and durable, given that existing smoking cessation treatments have relatively poor and often short-lived success rates.

Alternatively, an unblinded non-inferiority trial comparing a psychedelic to a highly effective treatment can also be causally informative—for example, a trial of psilocybin versus electroconvulsive therapy for TRD. Similar trials have been conducted for ketamine (Anand et al., 2023), though these are unlikely to attract funding before regulatory approval.

Much ink has been spilled in attempting to solve the thornier issue of controls for the psychosocial component of psychedelic trials, an entirely different question from the drug controls above. MDMA, and to a varying lesser extent, psilocybin, trials follow a drug-assisted psychotherapy paradigm in which the drug is meant to be a catalyst for psychological change via psychotherapy. While some have argued that, in psilocybin trials, the psychosocial intervention is or should be "psychological support" for safety rather than psychotherapy (Goodwin et al., 2024), others have argued that typical psilocybin therapy practices likely contain de facto psychotherapy (Nayak and Johnson, 2021). While "psychological support" is a coherent concept, it remains mostly unoperationalized in practice.

Investigating the psychosocial component, for example asking the question "does psychotherapy matter?" could be fruitful and would require an adequate control that demonstrably does not contain psychotherapy. Such a trial would need:

- An operational definition of psychotherapy, ideally agreed upon by intellectual adversaries.
- Recording and coding of session videos to confirm that, according to the operational definition, psychotherapy was not performed in the non-psychotherapy condition.
- Minimization of "integration" visits with psychotherapists.

Obviously, this may be less safe and/or effective but is nevertheless an important empirical question to answer. Safety concerns can be mitigated by maintaining a low threshold for aborting the psychedelic experience in the face of distress and prompt reintroduction of integration visits if any safety concerns (interpreted broadly) arise in the follow-up period.

Such a trial could compare the effects of psychotherapy to minimal support while also quantifying both the need for pharmacologic intervention to abort the experience and the need for reintroducing integration sessions. Our own speculation is that psychedelic therapy with minimal support will be less safe, less effective (but effective nonetheless), and less durable. But in the end, these are empirical questions that need to be addressed empirically. Ultimately, all control conditions are imperfect, and uncovering the truth will require triangulating evidence from multiple overlapping yet imperfect methodologies.

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References

Anand A, Mathew SJ, Sanacora G, et al. (2023) Ketamine versus ECT for nonpsychotic treatment-resistant major depression. *The New England Journal of Medicine* 388(25): 2315–2325.

Bedi G, Hyman D and de Wit H (2010) Is ecstasy an 'empathogen'? Effects of MDMA on prosocial feelings and identification of emotional states in others. *Biological Psychiatry* 68(12): 1134–1140.

Barnett BS, Anand A, Dewey EN, et al. (2024) Perceived risk of trying lysergic acid diethylamide in the United States from 2015 to 2019: Are Americans assessing lysergic acid diethylamide's risk profile more favorably? *Psychedelic Medicine (New Rochelle, N.Y.)* 2(2): 74–86.

Compass Pathways (2025) 'Compass Pathways Successfully Achieves Primary Endpoint in First Phase 3 Trial Evaluating COMP360 Psilocybin for Treatment-Resistant Depression', *Press Release*, 23 June. Available at: https://ir.compasspathways.com/News--Events-/news/news-details/2025/Compass-Pathways-Successfully-Achieves-Primary-Endpoint-in-First-Phase-3-Trial-Evaluating-COMP360-Psilocybin-for-Treatment-Resistant-Depression/default.aspx (accessed 20 August 2025).

Duru G and Fantino B (2008) The clinical relevance of changes in the Montgomery-Asberg Depression Rating Scale using the minimum clinically important difference approach. *Current Medical Research and Opinion* 24(5): 1329–1335.

Fedgchin M, Trivedi M, Daly EJ, et al. (2019) Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). *The International Journal of Neuropsychopharmacology* 22(10): 616-630.

Goodwin GM, Aaronson ST, Alvarez O, et al. (2023) Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life. *Journal of Affective Disorders* 327: 120–127.

Goodwin GM, Aaronson ST, Alvarez O, et al. (2025) The role of the psychedelic experience in psilocybin treatment for treatment-resistant depression. *Journal of Affective Disorders* 372: 523–532.

Goodwin GM, Malievskaia E, Fonzo GA, et al. (2024) Must psilocybin always "assist psychotherapy"? *American Journal of Psychiatry* 181(1): 20–25.

Holze F, Vizeli P, Müller F, et al. (2020) Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects. *Neuropsychopharmacology* 45(3): 462–471.

Kirkpatrick MG, Gunderson EW, Perez AY, et al. (2012) A direct comparison of the behavioral and physiological effects of methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology (Berl)* 219(1): 109–122.

Liechti ME, Dolder PC and Schmid Y (2017) Alterations of consciousness and mystical-type experiences after acute LSD in humans. *Psychopharmacology* 234(9-10): 1499–1510.

Molla H, Lee R, Lyubomirsky S, et al. (2023) Drug-induced social connection: Both MDMA and methamphetamine increase feelings of connectedness during controlled dyadic conversations. *Scientific Reports* 13(1): 15846.

Nayak S and Johnson MW (2021) Psychedelics and psychotherapy. *Pharmacopsychiatry* 54(4): 167–175.

Nayak SM, Bradley MK, Kleykamp BA, et al. (2023) Control conditions in randomized trials of psychedelics: An ACTTION systematic review. *The Journal of Clinical Psychiatry* 84(3): 22r14518.

Ochs-Ross R, Daly EJ, Zhang Y, et al. (2020) Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression-TRANSFORM-3. *The American Journal of Geriatric Psychiatry* 28(2): 121-141.

Popova V, Daly EJ, Trivedi M, et al. (2019) Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *The American Journal of Psychiatry* 176(6): 428-438.

Schuhmacher A, Hinder M, Brief E, et al. (2025) Benchmarking R&D success rates of leading pharmaceutical companies: An empirical analysis of FDA approvals (2006 2022). *Drug Discov Today* 30(2): 104291.

Sun D, Gao W, Hu H, et al. (2022) Why 90% of clinical drug development fails and how to improve it? *Acta Pharmaceutica Sinica. B* 12(7): 3049–3062.

US Food and Drug Administration (2024a) Psychopharmacologic Drugs Advisory Committee Meeting Briefing Document – Midomafetamine (MDMA) for PTSD. Silver Spring, MD: FDA. Available at: https://www.fda.gov/media/180463/download

US Food and Drug Administration (2024b) Psychopharmacologic Drugs Advisory Committee Meeting: Midomafetamine (MDMA) for PTSD [video]. Available at: https://www.youtube.com/watch?v=JqQKP8gcY1E (accessed 20 June 2024).

Vreman RA, Belitser SV, Mota ATM, et al. (2020) Efficacy gap between phase II and subsequent phase III studies in oncology. *British Journal of Clinical Pharmacology* 86(7): 1306–1313.

Yaden DB and Griffiths RR (2021) The subjective effects of psychedelics are necessary for their enduring therapeutic effects. *ACS Pharmacology & Translational Science* 4(2): 568–572.