Do Central Raters Remain Blinded in a Large Psychedelic Clinical Trial?

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SUBMISSION DETAILS

Request for Proposals Psychedelics

Abstract: Introduction: Maintaining rater blinding is a critical methodological consideration in clinical trials of psychoactive drugs, particularly for psychedelic compounds.1-2 While many psychiatric drugs face some degree of participant unblinding due to perceivable drug effects, whether adverse or intended, psychedelic drugs at therapeutic doses reliably produce profound, transient perceptual effects. This inherent characteristic of the drug category significantly increases the risk of participant and site functional unblinding, potentially undermining the interpretability of clinical trial outcomes. Although central raters (CRs) are not exposed to participants' transient drug experience, their blinding could still be compromised through spontaneous participant responses or by rating evaluations that show minimal or no indication burden. This study assessed whether CRs administering key endpoint assessments in a clinical trial of lysergide D-tartrate (LSD or MM120) remained blinded to participant treatment allocation.

Methods: Data were collected during a phase 2b multicenter, randomized, double-blind, placebo-controlled, dose-finding study (NCT05407064) evaluating MM120 in adults diagnosed with generalized anxiety disorder (GAD) and moderate-to-severe anxiety as defined by a Hamilton Anxiety Scale (HAM-A) of ≥20. Participants were randomized equally across 5 arms to receive a single dose of MM120 (25µg, 50µg, 100µg, 200µg) or placebo. At each study visit (Screening, Baseline, Weeks 1, 2, 4, 8, and 12), CRs were randomly assigned to participants to administer the HAM-A and Montgomery-Åsberg Depression Rating Scale (MADRS). CRs conducted evaluations via audio calls and were blinded to study information, including visit number, participant details, and treatment allocation. After completing both assessments during each visit, CRs completed the Rater Blinding Questionnaire (RBQ), a 5-point Likert scale: 1) I am certain the subject received the active drug; 2) I believe that the subject received the active drug; 3) I am unable to discern whether the subject received the active drug or placebo; 4) I believe the subject received placebo; or 5) I am certain the subject received placebo.

Results: The study screened 554 and randomized 198 participants. CRs completed 1586 unique

RBQs. In over 80% of RBQs collected from the Screening Visit to Week 12, CRs selected item 3, indicating that they were unable to determine treatment allocation. At Week 4, the study's primary endpoint, 71% of RBQs reported item 3, confirming CRs' inability to discern treatment allocation. Only 12% of assessments at Week 4 indicated that CRs were certain a participant had received active drug. This trend remained largely consistent as the dose of active drug increased, suggesting that the use of CRs effectively mitigated bias throughout the study.
Conclusion: This is the first large randomized controlled trial of a psychedelic drug to collect data on CR unblinding. Analysis of RBQs indicates most CRs were unable to distinguish active drug from placebo at the primary endpoint and throughout the trial. These findings support the use of CRs as a viable strategy to maintain blinding when assessing key endpoints in clinical trials of drugs with pronounced subjective effects. Future research should further explore the effectiveness of CR blinding, including interplay with participant and site staff potential unblinding, and the impact of maintaining blinding on CR and site rater outcome assessments, and potential impact on data interpretability.

Learning Objectives:

Learning Objective 1 To describe the methodological role of central raters in assessing key endpoints during trials of drugs with pronounced subjective effects.

Learning Objective 2 To evaluate whether central raters maintained blinding to treatment allocation in a study of MM120 (lysergide or LSD) for generalized anxiety disorder.

DISCLOSURE

Financial Relationships

Disclosure Yes, I do have a financial relationship(s) to disclose.

Financial Relationships Details

Ineligible Company	Type of Financial Interest
Mind Medicine Inc.	Employee