Functional Unblinding in Pivotal Studies and the Future of Psychedelic Medicine

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On June 4 of this year, the US Food and Drug Administration (FDA) convened an Advisory Committee to offer advice with respect to the evaluation of a new drug application from Lykos Therapeutics for midomafetamine (MDMA)-assisted psychotherapy, a treatment for posttraumatic stress disorder. The efficaciousness of the treatment as reflected in reported subject outcomes was substantial; one member of the advisory panel remarked that he had never seen such robust effect sizes, especially since these results were contrasted to the still rather good response of subjects who had the therapy alone. Such an effect against an active treatment was impressive in light of how many approved psychiatric medications simply edged out nonactive treatments, that is, a placebo. That advisor, however, recommended against approval, stating that the issue of "functional unblinding" led him to doubt what the data were claiming.

Functional unblinding refers to treatments whose effects are unmistakable, and thus, people who are assigned those treatments in a study would know whether they received the active study drug. This knowledge opens the door to the impact of subject expectation, that is, expectancy effects or the "placebo" effect, which powerfully influences study subjects' report of improvement. The inability to calculate the impact of functional unblinding on the reported efficacy outcome leads to uncertainty about the validity of clinical study data.

While listening to the discussion, and disappointed that the committee did not have an answer to the FDA's request for guidance on how to address this challenge, especially considering that a generation of new psychedelic therapeutics is in the pipeline, I considered the following thought experiment. If a treatment for a condition with unmet need (say, pain, depression, anxiety, sleep, suicidal thinking, etc) was observed to be 100% effective and safe but had an unmistakable physical signal (eg, notable nose tingling), would the general population be denied its availability? That would be unlikely; functional unblinding would be scrutinized but would not be an absolute barrier.

I do think the bar could be higher for a study drug that cannot be adequately blinded, and one could imagine enhanced guidelines or criteria for such an approval. The first requirement would be a plausible mechanism of action of the new treatment. The second would be having all subject assessments done by blinded remote raters trained to not elicit subject beliefs about treatment assignment. Third would be a robust effect size for response and remission. Fourth would be a favorable risk/benefit profile in terms of safety or potential risk mitigation. Fifth would be durability of response that would contrast with the natural history of a chronic or recurrent condition. And last, the agency could assess the "dry weight" of all prior data and human experience, including positive and negative testimonials. Taken together, these criteria provide a path forward to possible approval. I am quite confident from what I heard at the meeting that the FDA has thought these issues through and that, barring other gaps in a drug approval submission, there will be a path forward for novel treatments.

I had taken part in the presentation to the Advisory Committee only to speak to the issue of unmet need for patients. I assume no clinician would be pleased that novel treatments, with the potential to help many who have not been helped, would be unapprovable.

Article Information

Published Online: August 21, 2024. https://doi.org/10.4088/JCP.24com15504

J Clin Psychiatry 2024;85(3):24com15504

Submitted: July 9, 2024; accepted July 9, 2024.

To Cite: Rosenbaum JF. Functional unblinding in pivotal studies and the future of psychedelic medicine. *J Clin Psychiatry*. 2024;85(3):24com15504.

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Relevant Financial Relationships: Dr Rosenbaum has been an invited presenter for Lykos Therapeutics and is a cofounder and on the boards of directors of Entheos Labs and Sensorium Therapeutics.

Funding/Support: None.