The Use and Challenges of Placebo Use in Psychedelic Research: A Review

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ABSTRACT:

Background: Placebo-controlled trials (PCTs) of psilocybin have a high risk of functional unblinding, which challenges trial integrity. Currently, no consensus exists on the optimal choice of placebo for psychedelic trials. With the resurgence of interest in the therapeutic potential of psychedelics, there remains a need for thoughtful and innovative trial design.

Purpose: This review sought to assess placebo-controlled trials of psilocybin in terms of trial design, placebo choice, and blinding efficacy in order to identify the strengths and weaknesses of various trial designs and better inform future research.

Methods: A literature search was conducted to identify placebo-controlled trials published between January 1990 and August 2024 in which healthy individuals or those with mood, anxiety, or substance use disorders were given psilocybin as the primary intervention compared to a placebo. Definitions of placebo included inactive, active, and sub-therapeutic doses of psilocybin. Each trial was reviewed for trial design, placebo choice, blinding methodology, evidence of unintended unblinding, and other potential sources of bias.

Results: Nine trials were identified that met criteria for inclusion. Three trials (33%) evaluated psilocybin in the treatment of depression, two (22%) were for anxiety-related disorders, one (11%) for treatment of alcohol use disorder, and three (33%) were of healthy participants. Themes identified among multiple studies were the relative frequency of functional unblinding (formally evaluated in two (22%) and discussed as a limitation in at least two other trials (22%)), infrequency of blinding efficacy assessments, and heterogeneous trial designs and placebo choice (three (33%) with niacin, one (11%) with diphenhydramine, one (11%) with subtherapeutic psilocybin, and four (44%) with inactive placebo). Of the two trials (22%) that formally assessed blinding, one utilizing diphenhydramine and the other inactive placebo, both found a >93% accuracy rate for placebo group allocation.

Conclusions: Despite ongoing concerns about the risk of functional unblinding in psilocybin trials, blinding efficacy is infrequently assessed in any standardized way, and current trials do not provide evidence for an optimal placebo choice. Frameworks that incorporate allocation guessing, confidence ratings, and attribution assessments, such as one proposed by Szigeti et al., may offer a way to begin standardizing assessments. In order to improve the integrity and quality of future psilocybin trials, we recommend standardized inclusion of blinding efficacy assessments and continued innovation in trial designs that better account for expectancy effects.