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

Adam Cochran MS4, Johnathan Treem MD, Andrew Novick MD, PHD
University of Colorado Anschutz

BACKGROUND

- Randomized placebo-controlled trials (PCTs) attempt to separate a drug's pharmacological effects from the non-pharmacological effects associated with receiving a drug (placebo effect).
- The placebo effect is driven by patient expectations and contextual factors including patient-researcher dynamics and environmental cues.
- Expectancy is a particularly potent driver of the placebo effect arising from personal and cultural beliefs, attitudes toward treatment, and previous experiences.[1] Expectancy is highly variable and may inflate treatment effect estimates and false-positive risk.[1,2]
- Classical psychedelic compounds (e.g., psilocybin, LSD) act through serotonin type-2A (5-HT2A) agonism and produce potent acute subjective effects through marked alterations in perception and cognition, which are not replicated by inert or standard active placebos.[3,8]
- Research interest in psychedelics for the treatment of psychiatric disorders has grown in the past 2 decades. In that time researchers have noted that participants are at increased risk of becoming unblinded during these trials. For example, a 2022 crossover trial documented that participants accurately identified inert placebo 96% of the time.[5]
- Participants guessing their allocation during initial treatment (functional unblinding) may introduce bias when evaluating outcomes, such as the active treatment group over-reporting improvement outcomes (coined as activated expectancy bias by Szigeti et al.) or the inverse with the placebo group under-reporting improvements.[2]
- Functional unblinding appears to occur regardless of whether inactive or active placebos are utilized, and there currently is no consensus of an optimal placebo strategy or how to assess blinding efficacy.[2,5]

PURPOSE

This review seeks to assess PCT's of psilocybin in terms of trial design, placebo choice, and blinding efficacy in order to attempt to identify the strengths and weaknesses of various trial designs and better inform future research.

SEARCH METHODS

2.1. Eligibility criteria
This review included published placebo-controlled trials (PCTs) investigating the effects of psilocybin between January 1990 and August 2024. For inclusion we evaluated studies that were a) PCTs with placebos that were considered active, inactive, subtherapeutic dosing of psilocybin, b) included individuals who were either healthy or who had a psychiatric diagnosis including MDD, GAD, or a form of Substance use disorder (SUD) including Alcohol use disorder and Tobacco use disorder via DSM-IV or DSM-V criteria, c) utilized psilocybin as an experimental arm of treatment.

2.2 Exclusion Criteria:
Exclusion criteria were: a) trials without a placebo as the control condition, b) open-label trials.

2.3. Information Sources
Databases searched were PubMed, Web of Science, Google Scholar, Cochrane Library, and PsycInfo.

2.4. Search
Search terms specifying trial design of "Randomized Controlled Trial", "RCT", "placebo-controlled trial", "placebo" with an intervention of "psilocybin" or "psilocin" used with population identifiers including "depression", "anxiety", "GAD", "Alcohol use disorder", "Substance use disorder", "Tobacco use disorder".

2.5. Study selection
One investigator screened titles and abstracts for eligibility. This investigator met monthly with another experienced investigator to discuss trials for potential inclusion/exclusion. Investigators resolved disagreements around inclusion/exclusion through discussion.

REVIEWED TRIALS

Published Work	*Participant*	*Inclusion diagnosis*	***Trial Design***	*Trial Arms*	***Placebo Type***	***Placebo Drug***	*Primary Outcome*
Barrett et al., (2016)[17]	N=20, mean age = 28.5, 9M:11F	Healthy Adults with Hx of classic and dissociative hallucinogen use	Randomized, double-blind, **5-arm Crossover**	(1) placebo; (2-5) Psilocybin (10 mg, 20 mg, 30 mg, and 40 mg)	**Inactive placebo**	**Drug not specified**	Hourly subjective observer's rating of drug effects and neurocognitive measures
Bogenschutz et al., (2022)[18]	N=95, mean age = 45.8, 53M:42F	Alcohol dependence (SAMHSA definition).	Randomized, double-blind, **2-arm Parallel**	2 dosing sessions + psychological support. (1) Diphenhydramine 50–100 mg; (2) Psilocybin (25–40 mg/70 kg.	**Active placebo**	**diphenhydramine 50-100 mg**	percentage of heavy drinking days (PHDD) over 32 weeks
Carhart-Harris et al., (2021)[19]	N=59, mean age = 41.2, 39M:20F	moderate-to-severe MDD	Randomized, double-blind, **2-arm with active comparator (escitalopram)**	2 dosing sessions + psychological support. (1) Psilocybin 25 mg + daily placebo for 6 weeks; (2) Psilocybin 1 mg + daily Escitalopram 10–20 mg	**Sub therapeutic drug & inactive placebo**	**psilocybin 1 mg** **microcrystalline cellulose**	Change from baseline to week 6 of QIDS-SR-16. Also measured MADRS, HAM-D-17, BDI as secondary outcomes
Grob et al., (2011)[14]	N=12, age range 36-58 years. 1M:11F	advanced-stage cancer plus ASD, GAD, or acjustment disorder	Randomized, double-blind, **2-arm crossover**	1 dosing session + psychological support. (1) Niacin 250 mg (2) Psilocybin 0.2 mg/kg	**Active Placebo**	**Niacin 250 mg**	Change in STAI, BDI, POMS at 6 time points
Holze et al., (2022)[11]	N=28, mean age = 35, 14M:14F	Healthy Adults	Randomized, double-blind, **5-arm crossover**	(1) Placebo; (2) LSD 100 µg; (3) LSD 200 µg; (4) Psilocybin 15 mg; (5) Psilocybin 30 mg	**Inactive placebo**	**Mannitol and ethanol**	Subjective effects ratings (VAS, AMRS, 5D-ASC)
Raison et al., (2023)[20]	N=104, mean age = 41.1, 52M:52F	moderate-to-severe MDD	Multi-site, randomized, double-blind, **2-arm parallel**	1 dosing session + psychological support (1) Niacin 100 mg (2) Psilocybin 25 mg	**Active placebo**	**Niacin 100 mg**	Change in MADRS from baseline to day 43
Ross et al., (2016)[15]	N=29, mean age = 56.28, 11M:18F	Cancer-related acjustment disorder with anxious/depressed features	Randomized, double-blind, **2-arm crossover**	1 dosing session + psychological support. (1) Niacin 250 mg (2) Psilocybin 0.3 mg/kg	**Active placebo**	**Niacin 250 mg**	Change from baseline to 7 weeks and 26 weeks of HADS.
von Rotz et al., (2022)[21]	N=52, mean age = 36.75, 19M:33F	MDD	Randomized, double-blind, **2-arm parallel**	1 dosing session + psychological support (1) Placebo; (2) Psilocybin 0.215 mg/kg	**Inactive placebo**	**Mannitol**	Change from Baseline to day 14 for MADRS and BDI
Rucker et al., (2022)[22]	N=89, mean age = 36.1, 48M:41F	Healthy Adults	Randomized, double-blind, **3-arm parallel**	1 dosing session + psychological support. (1) Placebo; (2-3) Psilocybin 10 mg; and 25 mg	**Inactive placebo**	**Drug not specified**	Change in cognitive functioning assessed by (CANTAB) at days 8 and 29

Table 1. Overview of trial design and placebo choice

RESULTS

Blinding Efficacy
- Only 2/9 trials formally assessed blinding.
  - Bogenschutz et al. noted that across groups there was an approximately 94% correct guess rate for allocation.[6]
  - Holze et al. noted a 96% correct guess rate for placebo group allocation.[5]
- 3/9 studies mentioned evidence of unblinding in discussions.

Placebo choice
- 4/9 active placebo (3/9 niacin)
- 4/9 inactive placebo
- 1/9 sub-therapeutic psilocybin

Trial Design
- 4/9 crossover design
- 1/9 active comparator
- 4/9 parallel design

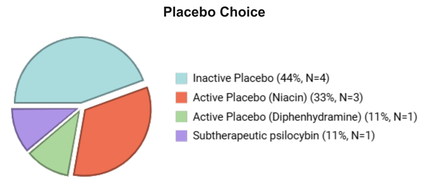

Figure 2: Placebo Choice in Trials
Created in https://BioRender.com

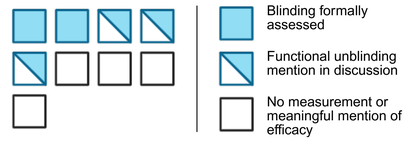

Figure 1: Presence of blinding assessments
Created in https://BioRender.com

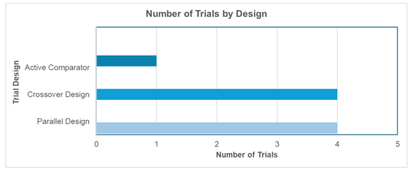

Figure 3: Number of trials by design

DISCUSSION/CONCLUSION

Functional Unblinding is frequently acknowledged, but rarely measured
- Of the 2/9 trials that formally assessed blinding, there was a >93% accurate placebo allocation guessing rate, suggesting a high rate of functional unblinding.[5,6]
- 3/9 of the remaining trials included examples of functional unblinding in their discussion, which suggests that this phenomenon is increasingly recognized, but not consistently assessed.

No Superior Placebo Strategy Can Be Identified
- Multiple trial design and placebo strategies are being explored concurrently.
- Heterogeneity in trial design, placebo choice, limited number of trials , and lack of consistent blinding efficacy measurements limit meaningful cross-study comparison
- These limitations prevent meaningfully determining a superior placebo choice

Consistent Blinding Efficacy Measures and Innovative Trial Designs are Needed
- Visual Analog Scales (VAS) and allocation guessing are simple and applicable methods for evaluating blinding efficacy.
- In addition to this, Szigeti et al. suggest this framework including a measure of how the participant attributes their ability to guess their allocation. This data may help guide future trial design.[2]

Potential Future Trial Designs
- Muthukumaraswamy et al. suggests parallel groups with active comparator, dose-response (subtherapeutic psilocybin as placebo), and balanced factorial trial designs as potentially viable.[4]
- 5-HT2A antagonist co-administration may be viable, although there is limited data on whether this abolishes therapeutic effects.
- Deception is potentially useful strategy for controlling for group belief states with careful ethics review. Miller et al. propose an "authorized deception" framework in which participants are made aware that aspects of the trial may be misleading.[7]

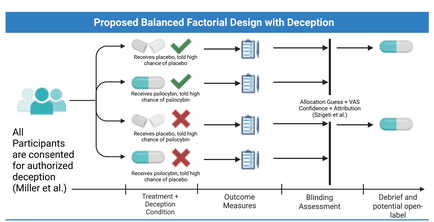

Figure 4: Proposed Balanced Factorial Design with Deception.
Created in https://BioRender.com

REFERENCES

1. Vallance AK. Something out of nothing: the placebo effect. Advances in Psychiatric Treatment. 2006;12(4):287-296. doi:10.1192/apt.12.4.287
2. Szigeti B, Nutt D, Carhart-Harris R, Erritzoe D. The difference between 'placebo group' and 'placebo control': a case study in psychedelic microdosing. Scientific Reports. 2023;13(1). doi:10.1038/s41598-023-34938-7
3. Brown RT, Nicholas CR, Cozzi NV, et al. Pharmacokinetics of Escalating Doses of Oral Psilocybin in Healthy Adults. Clinical Pharmacokinetics. 2017;56(12):1543-1554. doi:10.1007/s40262-017-0540-6
4. Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert Review of Clinical Pharmacology. 2021;14(9):1133-1152. doi:10.1080/17512433.2021.1933434
5. Holze F, Ley L, Müller F, et al. Direct comparison of the acute effects of lysergic acid diethylamide and psilocybin in a double-blind placebo-controlled study in healthy subjects. Neuropsychopharmacology. 2022;47(6):1180-1187. doi:10.1038/s41386-022-01297-2
6. Bogenschutz MP, Ross S, Bhatt S, et al. Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2022;79(10):953-962. doi:10.1001/jamapsychiatry.2022.2096
7. Miller FG, Wendler D, Swartzman LC. Deception in Research on the Placebo Effect. PLoS Medicine. 2005;2(9):e262. doi:10.1371/journal.pmed.0020262
8. Griffiths RR, Johnson MW, Richards WA, Richards BD, Mccann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology. 2011;218(4):649-665. doi:10.1007/s00213-011-2358-5

LIMITATIONS

- Restriction to PCT's possibly excluded other types of blinded RCT's that may have utilized standard of care rather than a placebo.
- These findings were intentionally focused on Psilocybin, and should not be assumed to likely extend to other psychedelics. Additional research would be needed to establish any overlap of findings.
- Having one investigator screen titles and abstracts may have introduced bias into the studies that were included, although we attempted to control for this through discussion.