Comparator selection in psychedelic clinical trial design

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Disclosures

- *Grant funding to RFMH*: Compass Pathways, Relmada, Marinus, Intracellular Therapies, Beckley Foundation, Ceruvia, Velocity Foundation (CUIMC; Markowitz PI)
- *Scientific advisory board*: Reset Pharmaceuticals
- *Honoraria*: Johns Hopkins U Press, Columbia U Press

Challenges of blinding psychedelic treatments

- Intense, often profound experiences with distinctive sensory/cognitive/emotional characteristics
- Combined medication and pharmacological treatment

  “set and setting”
- Standard placebo administration ensures nonblinding
- Difficulty matching physical and psychological experiences with putatively inactive treatments

Participant characteristics complicating comparator/blinding in psychedelic studies

- Expectation effects: highly educated/primed subjects; media/ Pollan etc.
- Prior psychedelic experience
- Suggestibility
- Comorbidities
- Nocebo effects/disappointment/ based on high expectations – especially with ‘no trip’ experiences, sometimes with active drug

Blinding and expectancy confounds in RCTs of psychedelics

- Average treatment effect (ATE) may be overestimated
- Placebo responses are mediated by belief and expectancy
- Psychedelic effects may be "*entirely due to … amplification of placebo response*" – *Strassman; Halpern*
- Assessing expectancy: *when? how? how often?*
- Masking: "essential aim is to prevent identification of the treatments until all such opportunities for bias have passed"
  - In psychedelic trials, "examination of maintenance of masking is rarely reported" and often not maintained
- Recommends clinical trials designs that are (and are not) appropriate for psychedelic RCTs– effectiveness/feasibility/cost?

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(Why) blinding is important in psychedelic studies

Proposed mechanism of action of psychedelics:

- Placebo hypothesis
- Mystical experience hypothesis
- Neuroplasticity hypothesis

Deficient blinding could lead to:

- Difficulty determining true efficacy
- Difficulty determining mechanism of action
- Unnecessary risk
  - medications with profound effects (and significant AEs) but potentially without real benefit

Is blinding possible in psychedelic studies?

- “Benign” unmasking: effects of intervention on the target disorder
- “Malicious” unmasking: side effects of the intervention
- Goal traditionally to “successfully control malicious masking”
- Psychedelics induce intense, obvious effects that are deemed essential to efficacy and difficult to duplicate
- Classic psychedelic studies: often do not assess success of masking; if assessed, rarely maintained

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Review of prior studies comparators

Study	Treatment Population	Drug	Subjects (N)[a]	Design and COMPARATOR	Active Dose(s)	# Active Treatment Sessions
CLINICAL TRIALS						
Grob et. al., 2011	Cancer patients with anxiety disorders	Psilocybin	12	Randomized crossover study with active placebo control (niacin)	0.2mg/kg	1
Griffiths et. al., 2016	Cancer patients with depression and/or anxiety symptoms	Psilocybin	51	Randomized crossover study with active placebo control (low-dose psilocybin)	0.31mg/kg, 0.43mg/kg	1
Ross et. al., 2016	Cancer patients with depression and/or anxiety	Psilocybin	29	Randomized crossover study with active placebo control (niacin)	0.3mg/kg	1
Davis et. al., 2020	Major depression	Psilocybin	24	RCT, patients randomized to either immediate or delayed treatment	0.29, 0.43mg/kg	2
Schindler et. al., 2020	Migraine headache	Psilocybin	10	Randomized crossover study with placebo control	0.14mg/kg	1
Carhart-Harris et. al., 2021	Major depression	Psilocybin	59	RCT, treatment arms escitalopram + psilocybin 1 mg *vs.* Psilocybin 25 mg	25 mg	2
Gasser et. al., 2014	Anxiety associated with life-threatening diseases	LSD	12	Randomized crossover study with active placebo control (low-dose LSD)	200mcg	2
Palhano-Fontes et. al., 2018	Treatment-resistant depression	Ayahuasca	29	RCT with active placebo control (placebo with unpleasant taste, induced nausea)	0.36mg/kg N, N-DMT	1
Dos Santos et al., 2021	Social anxiety disorder	Ayahuasca	17	RCT with active placebo control (organoleptic placebo)	2mL/kg	1
Goodwin et. al., 2022	Treatment-resistant depression	Psilocybin	233	RCT with active placebo control (low dose psilocybin)	1, 10, 25 mg	1
Holze et. al., 2022	Anxiety/+/- life threatening illness	LSD	42	RCT with 2 doses LSD or placebo	LSD (200 µg)	2
Bogenschutz et al., 2022	Alcohol Use Disorder	Psilocybin	95	RCT with active placebo control (Diphenhydramine)	25mg/kg	2
Schindler et al., 2022	Cluster Headache	Psilocybin	16	Randomized crossover study to receive placebo (microcrystalline cellulose), low, or high dose psilocybin	0.143 mg/kg	3

Updated, from Bender & Hellerstein 2022

Options to date:
13 published RCTs of classic psychedelics in modern era

- Placebo caps/pills: *Schindler; Liechti; Holze*
- Nonpsychedelic medications with effects/side effects
  - Niacin: *Grob, Ross*
  - "Placebo with unpleasant taste": *Palhano-Fontes*
  - Methylphenidate: *Griffiths*
- Low-dose psychedelic
  - e.g. 1 mg PSI, 25 mcg LSD: *Griffiths; Griffiths; Gasser; Hasler*
- Other psychedelic medication
  - Dextromethorphan: *Carbonaro*
- Crossover design; delayed treatment design

Success rate of blinding

- **Niacin:** Study staff guessed tx condition correctly in 97% of cases (Ross et al., 2016)
- **Low dose (LSD):** 100% participants and 96% therapists guessed tx assignment correctly (Gasser et al., 2015)
- **Low dose (psilocybin):** All correctly guessed psilocybin had been administered but most guessed the drug or dose conditions incorrectly* (Griffith et al, 2016; 2018)
- **Methylphenidate:** 77% of sessions guessed correctly by study therapists (Griffiths et al, 2006)

Bender & Hellerstein 2022

Blinding in ongoing clinical studies with comparators *(N=41)*

Categories	LSD	Psilocybin	Total (*N*=41)
Inactive placebo	3	14	17
Active placebo	0	11	11
Active comparator	2	5	7
Waitlist	0	5	4
Alternative intervention	0	3	3
Total	**5**	**38**	**42***

* Note: One study has more than one comparator

Of 90 ongoing studies of clinical populations (81 PSI, 5 LSD, 2 DMT, 2 5MEO-DMT)

Review of Clinicaltrials.gov 2/2024

Detail of comparators in 41 ongoing studies

Categories	Sub-categories	LSD	Psilocybin	Total (*N*=41)
Inactive Placebo (*n*=17)	Microcrystalline cellulose	0	6	6
	Mannitol	0	1	1
	Starch 1500	0	1	1
	Lactose	0	1	1
	Matching placebo (0mg; not defined)	3	5	8
Active placebo (*n*=11)	Niacin / nicotinamide	0	7	7
	Diphenhydramine (antihistamine)	0	2	2
	Benzodiazepine (Lorazepam 1mg; Midazolam 5mg)	0	2	2
Active comparator (*n*=7)	Low dose *	2	2	4
	Ketamine	0	2	2
	Dextromethorphan (cough suppressant)	0	1	1
Waitlist (*n*=4)		0	4	4
Alternative intervention (*n*=3)	Nicotine Replacement Therapy	0	1	1
	Mindfulness-Based Stress Reduction	0	1	1
	Treatment-as-usual	0	1	1
Total		**5**	**38**	**42****

* psilocybin: 1mg; LSD: 10µg, 25 µg

** Note: One study has more than one comparator

Assessments to ensure integrity of blinding

- Assessing participant/staff/rater guesses re treatment assignment
  - potential drawbacks
- Blinded remote raters – how successful?
- Excluding subjects with prior psychedelic use
- De-emphasize drug name/identification in recruitment materials:
  - ‘5HT2A agonist’ rather than ‘Psilocybin’ or ‘LSD’
- Other measures

Comparator choice: *depends on goal of study*

Primary medication options

- Placebo
- Low dose psychedelic
- Amphetamine
- Niacin

Proposed additional options: minimal data

- Psychedelic dose with minimal therapeutic properties:
  - e.g. psilocybin 10 mg ← *new option: +/-*
- Mind-altering/psychedelic-experience-inducing drug without 5HT2A activity – if without therapeutic efficacy
- Virtual reality (VR) +/- medication: Aday 2020 ← *new option*
- Induction of amnesia/general anesthesia: Raison
- Block psychedelic experiences but not neural network effects (?)
  - Quetiapine, nuplazid

Summary/Conclusions

- Complexity of psychedelic treatments
  - Combined medication and psychotherapy
  - Centrality of expectation for therapeutic benefit
- Difficulty masking psychedelic drug effects
- Potential choices to mimic “benign” and/or “malicious” effects
- Need for innovative solutions including:
  - Novel trial design
  - Additional comparators
- *Unclear feasibility, cost, success of such approaches*
- *Potential benefits clarifying efficacy, mechanism, risks*

References

- Aday JS, Davoli CC, Bloesch EK. Psychedelics and virtual reality: parallels and applications. Therapeutic Advances in Psychopharmacology. 2020 Aug;10:2045125320948356.
- Bogenschutz MP, Ross S, Bhatt S, Baron T, Forcehimes AA, Laska E, Mennenga SE, O'Donnell K, Owens LT, Podrebarac S, Rotrosen J. 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 Oct 1;79(10):953-62.
- Bender D, Hellerstein DJ. Assessing the risk–benefit profile of classical psychedelics: A clinical review of second-wave psychedelic research. Psychopharmacology. 2022 Jan 13:1-26.
- Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, Martell J, Blemings A, Erritzoe D, Nutt DJ. Trial of psilocybin versus escitalopram for depression. New England Journal of Medicine. 2021 Apr 15;384(15):1402-11.
- Carbonaro TM, Johnson MW, Hurwitz E, Griffiths RR. Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: similarities and differences in subjective experiences. Psychopharmacology. 2018 Feb;235:521-34.
- Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, Finan PH, Griffiths RR. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA psychiatry. 2021 May 1;78(5):481-9.
- Dos Santos RG, Rocha JM, Rossi GN, Osório FL, Ona G, Bouso JC, Silveira GD, Yonamine M, Marchioni C, Crevelin EJ, Queiroz ME. Effects of ayahuasca on the endocannabinoid system of healthy volunteers and in volunteers with social anxiety disorder: Results from two pilot, proof-of-concept, randomized, placebo-controlled trials. Human Psychopharmacology: Clinical and Experimental. 2022 Jul;37(4):e2834.

References

- Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T, Brenneisen R. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. The Journal of nervous and mental disease. 2014 Jul;202(7):513.
- Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, Bird C, Blom RE, Brennan C, Brusch D, Burke L. Single-dose psilocybin for a treatment-resistant episode of major depression. New England Journal of Medicine. 2022 Nov 3;387(18):1637-48.
- Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, Cosimano MP, Klinedinst MA. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. Journal of psychopharmacology. 2016 Dec;30(12):1181-97.
- Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology. 2006 Aug;187:268-83.
- Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, Greer GR. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Archives of general psychiatry. 2011 Jan 3;68(1):71-8.
- Holze F, Gasser P, Müller F, Dolder PC, Liechti ME. Lysergic acid diethylamide–assisted therapy in patients with anxiety with and without a life-threatening illness: a randomized, double-blind, placebo-controlled phase II study. Biological Psychiatry. 2023 Feb 1;93(3):215-23.
- Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert review of clinical pharmacology. 2021 Sep 2;14(9):1133-52
- Palhano-Fontes F, Barreto D, Onias H, Andrade KC, Novaes MM, Pessoa JA, Mota-Rolim SA, Osório FL, Sanches R, Dos Santos RG, Tófoli LF. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychological medicine. 2019 Mar;49(4):655-63.

References

- Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, Mennenga SE, Belser A, Kalliontzi K, Babb J, Su Z. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. Journal of psychopharmacology. 2016 Dec;30(12):1165-80.
- Schindler EA, Sewell RA, Gottschalk CH, Luddy C, Flynn LT, Lindsey H, Pittman BP, Cozzi NV, D'Souza DC. Exploratory controlled study of the migraine-suppressing effects of psilocybin. Neurotherapeutics. 2021 Jan;18(1):534-43.
- Schindler EA, Sewell RA, Gottschalk CH, Luddy C, Flynn LT, Zhu Y, Lindsey H, Pittman BP, Cozzi NV, D'Souza DC. Exploratory investigation of a patient-informed low-dose psilocybin pulse regimen in the suppression of cluster headache: Results from a randomized, double-blind, placebo-controlled trial. Headache: The Journal of Head and Face Pain. 2022 Nov;62(10):1383-94.
- Strassman R. The political correction of psychedelics. Part 3. Psychedelics as Super-Placebos 2017