Control Conditions in Randomized Trials of Psychedelics: An ACTTION Systematic Review

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ABSTRACT

Objective: To systematically review control conditions of all available randomized psychedelic trials.

Data Sources: We searched PubMed, PsycINFO, and EMBASE for randomized trials of psychedelics in humans from 1940 through May 2020 with no language restrictions. PRISMA guidelines were followed. (PROSPERO registration number: PROSPERO-CRD42020205341.)

Study Selection: All randomized trials of psychedelics in humans from 1940 through May 2020 were included.

Data Extraction: Two independent reviewers performed extraction. Extracted data included study design, demographics, blinding type, whether and how blind integrity was assessed, psychedelic used and dose, drug control condition and dose, type of non-drug control condition, number of dosing sessions, and recruitment source. Outcome data were not collected.

Results: In total, 126 articles were included, encompassing 86 unique studies. Of studies with a drug control condition (80), 49 (61.2%) used an inert placebo control, 16 (20.0%) used active comparators, 12 (15.0%) used both, and 3 (3.8%) used only different active psychedelic doses as a control. Only 3 of 21 therapeutic trials compared the use of psychological support to a minimally supportive condition. The majority (81/86; 94%) of studies were blinded, though only 14 (17.3%) included blind assessment; only 8 of these 14 studies assessed participants' blinding. Blinding success, assessed in highly varied ways, was generally poor.

Conclusions: Randomized psychedelic trials underutilize elements that would improve quality or provide important information: blind assessment, active drug controls, and testing psychological support against minimal-support conditions. Several queried categories, including blind integrity assessment and details of non-drug control conditions, were insufficiently reported by many reviewed studies. Recommendations are provided to improve trial methods.

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Psychedelics have garnered a great deal of enthusiasm as therapeutic agents because clinical trials have shown preliminary evidence of efficacy for diverse medical conditions.[1–7] While randomized controlled trials have been performed with psychedelic drugs, several methodological concerns have been raised regarding the adequacy of existing control conditions in psychedelic trials.[8,9] These include unblinding due to powerful subjective effects and high levels of interpersonal support (in therapeutic trials) that make it hard to disentangle direct drug effects from nonspecific support effects. The hypothesis that psychedelics exert therapeutic effects through subjective effects in a manner similar to psychotherapy[10,11] further complicates the design of appropriate control conditions. Moreover, psychedelic trials may serve different goals, in some cases seeking to gain an understanding of the real-world utility of the entirety of the intervention (pharmacologic and non-pharmacologic), in other cases attempting to disentangle direct drug therapeutic effects from other non-drug elements or to elucidate mechanisms, and yet in other trials seeking to provide data for regulatory approval.

Unblinding is concerning, as expectations may cause therapeutic effects that are conflated with active intervention effects in addition to other forms of bias. In contrast, unblinding caused by therapeutic effects is significantly less inferentially problematic (though may nonetheless introduce researcher bias). These two types of unblinding (termed "malicious" and "benign," respectively) can be difficult to disentangle.[9]

Possible solutions for poor blinding in these trials include using active comparators, assessing blinding success,[9] and identifying predictors of blind maintenance. Across studies, alternative designs such as open-label comparative efficacy studies provide complementary information. Possible solutions to the problem of disentangling general psychotherapeutic effects from medication effects can include the administration of psychedelics with differing levels of psychological support (with the minimum required for safety)[11] or even while the patient is anesthetized,[10] or the measurement of common psychotherapeutic change mechanisms shown to be predictive of beneficial effects.[9,11,12] However, the extent to which these strategies have been used has not been systematically examined.

These methodological problems risk rendering psychedelic clinical trials underinformative. This

Clinical Points

- Although randomized controlled trials have been performed with psychedelic drugs, several methodological concerns have been raised regarding the adequacy of existing control conditions in psychedelic trials, include unblinding due to powerful subjective effects and high levels of interpersonal support (in therapeutic trials) that make it hard to disentangle direct drug effects from nonspecific support effects.
- Randomized psychedelic trials underutilize elements that would improve quality or provide important information, such as blind assessment, active drug controls, and testing psychological support against minimal-support conditions.

systematic review aims to survey and assess control conditions of randomized trials of classic psychedelics. In addition to summarizing this work, this review used these findings to produce a set of recommendations for optimizing the design of future research.

METHODS

Data were collected in accordance with PRISMA guidelines.[13] This project was submitted for preregistration to Prospero on August 28, 2020, and was registered September 27, 2020, and it is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=205341.

Search Strategy and Selection Criteria

Search terms were selected to maximize collection of relevant reports. The databases PubMed, PsycINFO and EMBASE were searched for randomized trials of classic psychedelics in humans. See Supplementary Appendix 1 for full search terms for each database. There were no language restrictions, and the search encompassed from 1940 through May 2020. The electronic search was supplemented by hand searching other sources including other systematic reviews on the topic of psychedelics.

The online application Covidence was used to automatically remove duplicates and to code during the extraction phase. Full text extraction took place between August 28, 2020, and April 30, 2021. Two authors (S.M.N. and M.K.B.) independently reviewed and coded articles and resolved discrepancies by discussion. A third author (B.A.K.) arbitrated in the event of disagreements not resolved by one-on-one discussion.

We included randomized trials dosing human participants with a classic psychedelic (defined as a 5-HT_{2A} agonist). There were no restrictions based on participant population, language, or time of publication (assuming that no studies preceded 1940).

Data Extraction

Extracted data included (when available) study design, number of participants, demographics, type of blinding, whether and how blind integrity was assessed, psychedelic used and dose, drug control condition used and dose, type of non-drug control condition, number of dosing sessions, and recruitment source. Outcome data were not collected.

Both therapeutic and nontherapeutic studies were included. Studies were coded as therapeutic if they investigated a psychedelic as a therapeutic in a clinical population. Several additional categories were coded only for therapeutic studies. These included whether therapeutic effects of individual monitors (the term *monitor* is used here, but these staff were variously called guides, facilitators, therapists, etc) were assessed, and the number and hours of preparation and integration sessions. Monitors are individuals who are typically present with participants in preparation, dosing, and integration sessions. Preparation sessions were defined as non-drug meetings prior to a dosing session and served the purpose of building rapport, educating participants on drug effects, and developing and clarifying therapeutic intentions. Integration sessions were defined as non-drug meetings following a dosing session that focused on interpreting or otherwise utilizing the content of the session.

Studies that included a placebo but did not explicitly mention blinding were presumed single-blind.

The number of participants was coded as number randomized. One study[14] reported a "control group" composed of individuals receiving treatment as usual (via retrospective chart review) who had not been recruited into the study—these were not counted as participants.

Study quality assessments were not performed, as outcome data were not collected.

Data Analysis

No statistical procedures were employed other than calculating means, standard deviations, and percentages.

RESULTS

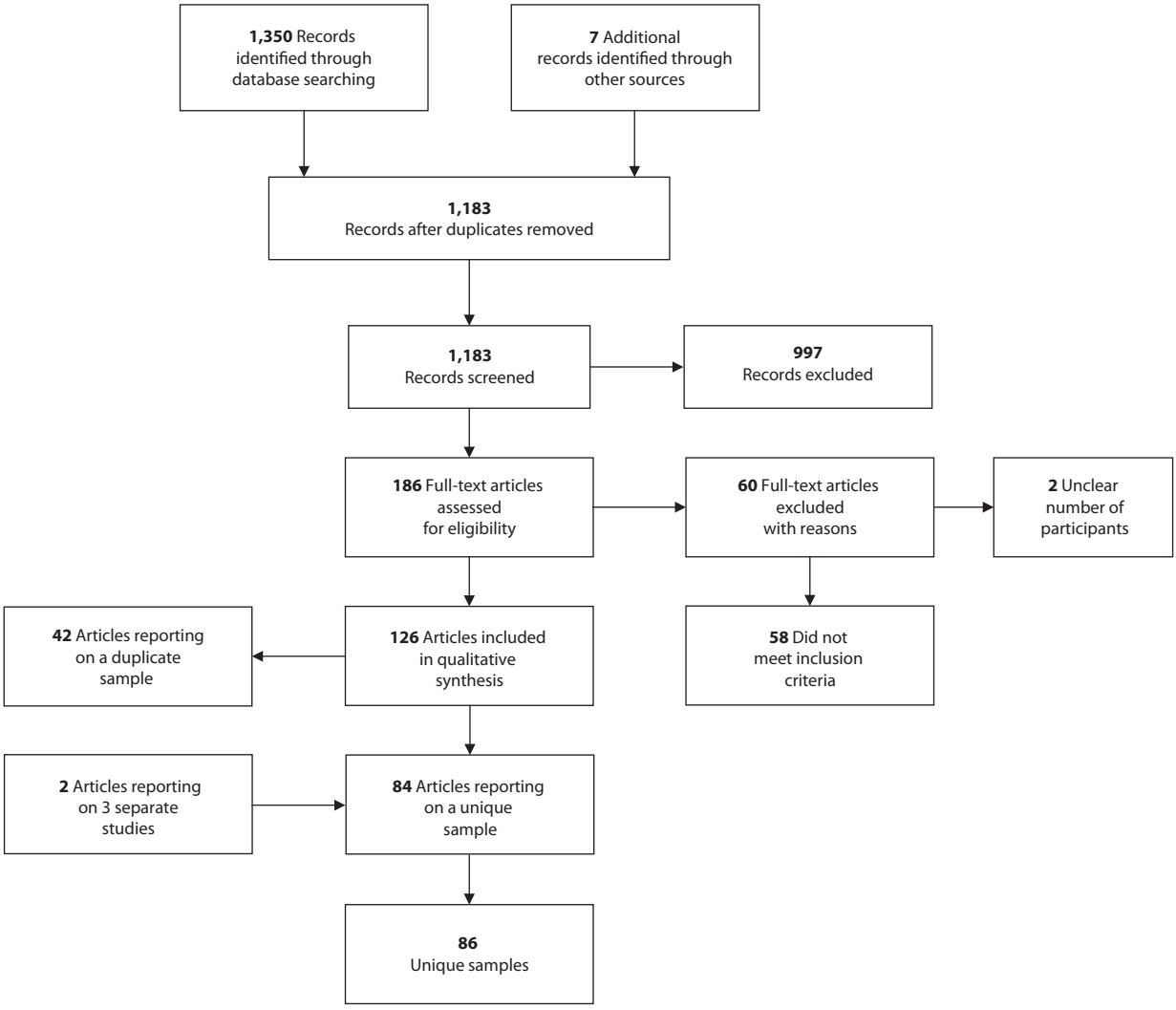
A total of 1,350 articles met initial search criteria (Figure 1). An additional 7 studies were found manually.[15–21]

One hundred seventy-four duplicates were automatically removed. A total of 997 articles were screened out at the title and abstract phase as they did not meet inclusion criteria. Fifty-eight studies were excluded at full text review, as they also did not meet inclusion criteria. Two articles were excluded due to an unclear number of participants in the study and in each dose condition.[22,23] This left 126 articles for extraction.

We found that 21 datasets were used as the basis of multiple articles in this sample of 126. A total of 42 articles in this sample were derived from data that formed the basis of another study. These included, for example, imaging studies or secondary analyses of an original parent study. In these cases, the parent article was coded, and the duplicate articles were simply tagged as such and not included in the present analyses.

Two articles each reported on 2 separate randomized studies, and these were coded as separate studies.[24,25]

Figure 1. PRISMA Flow Diagram for Study Selection



Excluding the 42 duplicate articles, and including the 4 studies reported in the 2 articles that contained 2 separate randomized studies,[24,25] there were a total of 86 unique studies coded in this sample. This is described in the PRISMA flowchart (Figure 1).

Demographics

There was a mean (SD) of 34.5 (34.9) participants (range, 3–176) in the 86 studies ranging from 1963 to 2020. Seventy-nine studies (91.9%) reported on sex. Of these, males comprised 71.3% of the total sample.

The plurality of the 86 studies was conducted in the United States (31; 36%) followed by Switzerland (26; 30.2%), Spain (8; 9.3%), the UK (7; 8.1%), Germany (4; 4.7%), Brazil (3; 3.5%), Canada (3; 3.5%), the former Czechoslovakia (1; 1.2%), Czech Republic (1; 1.2%), Netherlands (1; 1.2%), and Sweden (1; 1.2%). Only 12 studies (14%) reported the racial composition of participants. Of the total number of participants in these 12 studies, White people comprised 73.8%.

Forty-seven (54.7%) of the studies reported prior use of psychedelics. Of the total number of participants in these studies, 53.8% had previously used psychedelics.

Study Design

Study designs (see Table 1) were as follows regarding the comparison between the psychedelic and control condition: 53 within-subjects crossover, 24 between-subjects, and 9 between-subjects with within-subjects crossover (this latter category involved randomized parallel groups that then crossed over to the other condition[s]).

The following drugs were investigated in these studies: psilocybin, 36 (41.9%); lysergic acid diethylamide (LSD), 33 (38.4%); ayahuasca 10 (11.6%); dimethyltryptamine (DMT) (other than ayahuasca), 6 (7%); dipropyltryptamine (DPT), 2 (2.3%); mescaline, 1 (1.2%); and 6-HDMT (6-hydroxy-*N*-dimethyltryptamine), 1 (1.2%). There was some overlap, as 1 study included mescaline,[25] LSD, and psilocybin and another included DMT and 6-HDMT.[90]

Table 1. Studies Included in the Systematic Review[a]

Publication	n	Experiment Number[b]	Study Design	Sample	Psychedelic	Drug Comparator	Non-Drug Comparator
Holze et al (2020)[26]	28		Double-blind within-subjects crossover	Healthy volunteers	LSD	Placebo, MDMA, and D-amphetamine	
Holze et al (2019)[27]							
Wittmann et al (2007)[28]	12		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo and different doses of psilocybin	
Wackermann et al (2008)[29]		1					
Preller et al (2017)[30]	25		Double-blind within-subjects crossover	Healthy volunteers	LSD	Pretreatment with ketanserin. Treatment compared with placebo	
Kraehenmann et al (2017)[31]							
Kraehenmann et al (2017)[32]							
Preller et al (2018)[33]							
Preller et al (2018)[34]							
Barrett et al (2018)[35]							
Preller et al (2019)[36]							
Pokorny et al (2020)[37]							
Jaffe et al (1972)[38]	7		Double-blind between-subjects	Healthy psychotherapy patients	LSD	Placebo, dextroamphetamine	
Jaffe et al (1973)[39]							
Dahlberg and Jaffe (1979)[40]							
Natale et al (1979)[41]							
Mueller et al (2017)[42]	24		Double-blind within-subjects crossover	Healthy volunteers	LSD	Placebo	
Dolder et al (2016)[43]		1					
Liechti et al (2017)[44]		1					
Dolder et al (2017)[45]							
Müller et al (2017)[46]							
Müller et al (2018)[47]							
Schmidt et al (2018)[48]							
Schmid et al (2015)[49]	16		Double-blind within-subjects crossover	Healthy volunteers	LSD	Placebo	
Dolder et al (2016)[43]		2					
Strajhar et al (2016)[50]							
Liechti et al (2017)[44]		2					
Schmid and Liechti (2018)[51]							
Strassman and Qualls (1994)[52]	12		Double-blind within-subjects crossover	Experienced hallucinogen users	DMT	Saline placebo and different doses of DMT	
Strassman et al (1994)[53]							
Riba et al (2003)[54]	18		Double-blind within-subjects crossover	Experienced psychedelics users	DMT	Placebo, and different doses of ayahuasca	
Riba, Anderer, et al (2002)[55]							
Riba et al (2002)[56]							

(continued)

Table 1 (continued).

Publication	n	Experiment Number[b]	Study Design	Sample	Psychedelic	Drug Comparator	Non-Drug Comparator
Ludwig and Levine (1965)[57]	70		Single-blind between subjects	"Post-narcotic drug addict inpatients"	LSD		Hypnosis; psychotherapy; hypnosis + psychotherapy with or without drug
Levine and Ludwig (1965)[58]							
Palhano-Fontes et al (2019)[59]	30		Double-blind between subjects	Treatment-resistant depression	Ayahuasca	Liquid mixture including zinc to produce gastrointestinal distress, designed to look and taste like ayahuasca	
Zeifman et al (2019)[60]							
Galvão et al (2018)[61]	71		Double-blind between subjects	Treatment-resistant depression and healthy controls	Ayahuasca	Placebo	
Almeida et al (2019)[62]							
Smigielski, Kometer, et al (2019)[63]	40		Double-blind between subjects	Buddhist meditators	Psilocybin	Placebo	
Smigielski, Scheidegger, et al (2019)[64]							
Yanakieva et al (2019)[65]	48		Double-blind between subjects	Healthy volunteers	LSD	Placebo and different doses of LSD	
Family et al (2020)[66]							
Kometer et al (2012)[67]	17		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo and ketanserin pretreatment	
Kometer et al (2013)[68]							
Kometer et al (2015)[69]		1					
Pokorny et al (2016)[70]	40		Double-blind between subjects with within-subjects crossover	Healthy volunteers	Psilocybin	Placebo and pretreatment with ergotamine and buspirone	
Kometer et al (2015)[69]		2					
Kometer et al (2015)[69]		3					
Griffiths et al (2011)[71]	18		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo and different doses of psilocybin	
Johnson et al (2012)[72]							
Gouzoulis-Mayfrank et al (2005)[73]	15		Double-blind within-subjects crossover	Healthy volunteers	DMT	Different doses of DMT vs *S*-ketamine	
Gouzoulis-Mayfrank et al (2006)[74]							
Heekeren et al (2007)[75]							
Heekeren et al (2008)[76]							
Gouzoulis-Mayfrank et al (1999)[77]	32		Double-blind between-subjects	Healthy volunteers	Psilocybin	MDE, methamphetamine, placebo	
Gouzoulis-Mayfrank et al (1998)[78]							
Gouzoulis-Mayfrank et al (1999)[79]							
Gouzoulis-Mayfrank et al (2002)[80]							
Kraehenmann et al (2015)[81]	25		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo	

(continued)

Table 1 (continued).

Publication	n	Experiment Number[b]	Study Design	Sample	Psychedelic	Drug Comparator	Non-Drug Comparator
Grimm et al (2018)[82]							
Daumann et al (2008)[83]	14		Double-blind within-subjects crossover	Healthy volunteers	DMT	*S*-ketamine and placebo	
Daumann et al (2010)[84]							
Carbonaro et al (2018)[85]	21		double-blind within-subjects crossover	Healthy volunteers	Psilocybin	DXM, placebo, different doses of psilocybin	
Barrett et al (2018)[86]							
Bershad et al (2019)[87]	20		Double-blind within-subjects crossover	Healthy volunteers	LSD	Placebo and different doses of LSD	
Bershad et al (2020)[88]							
Natale et al (1978)[89]	3		Double-blind within-subjects crossover	"Neurotic depressed" psychoanalytic outpatients	LSD	Dextroamphetamine 15 mg, placebo	
Hollister et al (1962)[25]	4	1	Single-blind within-subjects crossover	Psychotherapy patients	Psilocybin	Placebo and different doses of psilocybin	
Hollister et al (1962)[25]	18	2	Single-blind within-subjects crossover	Psychotherapy patients	Mescaline, psilocybin, and LSD	Mescaline, psilocybin, and LSD	
Rosenberg et al (1964)[90]	6		Single-blind within-subjects crossover	Incarcerated former opiate addicts	DMT and 6-HDMT	Placebo; 6-HDMT	
Vollenweider et al (1999)[91]	7		Single-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo	
Netz et al (1963)[92]	8		Single-blind within-subjects crossover	Healthy volunteers	LSD	Placebo	
Dolezal and Hausner (1968)[93]	8		Double-blind within-subjects crossover	"Neurotic inpatients"	LSD	Benactyzine 25 mg; phenmetrazine 10 mg SQ	
Hasler et al (2004)[94]	8		Double-blind within-subjects crossover	Healthy volunteers (university and hospital staff)	Psilocybin	Placebo and different doses of psilocybin	
Carter et al (2005)[95]	8		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo and ketanserin	
Moreno (2006)[96]	9		Double-blind within-subjects crossover	Obsessive-compulsive disorder	Psilocybin	Different doses of psilocybin	
dos Santos et al (2007)[97]	9		Double-blind between-subjects with within-subjects crossover	Experienced long-term ayahuasca users	Ayahuasca	Placebo	
Vollenweider et al (1998)[24]	10	1	Single-blind between-subjects with within-subjects crossover	Healthy volunteers	Psilocybin	Pretreatment with ketanserin, haloperidol, risperidone or placebo. Treatment compared with placebo	
Vollenweider et al (1998)[24]	15	2	Single-blind between-subjects with within-subjects crossover	Healthy volunteers	Psilocybin	Pretreatment with ketanserin, treatment compared with placebo	
Dos Santos et al (2011)[98]	10		Double-blind within-subjects crossover	Healthy volunteers	Ayahuasca	Placebo, *d*-amphetamine	
Alonso et al (2015)[99]	10		Double-blind within-subjects crossover	Healthy volunteers	Ayahuasca	Placebo	

(continued)

Table 1 (continued).

Publication	n	Experiment Number[b]	Study Design	Sample	Psychedelic	Drug Comparator	Non-Drug Comparator
Carter et al (2005)[100]	12		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo and different doses of psilocybin	
Grob et al (2011)[101]	12		Double-blind within-subjects crossover	Patients with advanced cancer and anxiety	Psilocybin	Niacin 250 mg	
Gasser et al (2014)[102]	12		Double-blind between-subjects	Patients with anxiety associated with life-threatening diseases	LSD	Low-dose LSD 20 µg	
Valle et al (2016)[103]	12		Double-blind within-subjects crossover	Healthy volunteers	Ayahuasca	Pretreatment with ketanserin. Treatment compared with placebo	
Strassman et al (1996)[104]	13		Double-blind within-subjects crossover	Healthy volunteers	DMT	IV saline	
Riba et al (2006)[105]	15		Double-blind within-subjects crossover	Experienced psychedelics users	Ayahuasca	Placebo	
Carhart-Harris et al (2012)[106]	15		Single-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo (IV saline)	
Vollenweider et al (2007)[107]	16		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo and different doses of psilocybin	
Quednow et al (2012)[108]	16		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo and ketanserin	
Kometer et al (2011)[109]	17		Single-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo, different doses of psilocybin	
Dos Santos et al (2012)[110]	17		double-blind within-subjects crossover	Healthy volunteers	Ayahuasca	Placebo	
Soskin et al (1973)[111]	18		Double-blind within-subjects crossover	"Alcoholics"	DPT	Inactive placebo IM	
Umbricht et al (2003)[112]	18		Single-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo	
Riba et al (2004)[113]	18		Double-blind within-subjects crossover	Experienced psychedelic users	Ayahuasca	Placebo	
Tagliazucchi et al (2016)[114]	20		single-blind within-subjects crossover	Healthy volunteers	LSD	Placebo (IV saline)	
Speth et al (2016)[115]	20		Single-blind within-subjects crossover	Healthy volunteers	LSD	Saline placebo IV	
Timmermann et al (2018)[116]	20		Single-blind within-subjects crossover	Healthy volunteers	LSD	Placebo (IV saline)	
Bravermanová et al (2018)[117]	20		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo	
Barbanoj et al (2008)[118]	22		Double-blind within-subjects crossover	Healthy volunteers	Ayahuasca	Placebo and *d*-amphetamine	
Preller et al (2020)[119]	23		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo	
Soskin (1973)[21]	28		Double-blind between subjects	"Psychosomatic" and "nonpsychotic inpatients"	LSD	Chlordiazepoxide 25 mg and methylphenidate 25 mg	
Ross et al (2016)[5]	29		Double-blind between subjects with within-subjects crossover	Anxiety and depression in cancer	Psilocybin	Niacin 250 mg (active placebo)	

(continued)

Table 1 (continued).

Publication	n	Experiment Number[b]	Study Design	Sample	Psychedelic	Drug Comparator	Non-Drug Comparator
Preller et al (2016)[120]	29		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo	
Smart et al (1966)[121]	30		double-blind between-subjects	"Alcoholics"	LSD	Ephedrine 60 mg	Psychosocial treatment as usual
Bernasconi et al (2014)[122]	30		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo	
Zegans (1967)[123]	31		Single-blind between subjects	Healthy volunteers	LSD	Placebo	
Wikler et al (1965)[124]	33		Single-blind within-subjects crossover	"Postaddicts"	LSD	Placebo IM, morphine IM, pentobarbital IM, amphetamine IM	No treatment control groups of (1) research staff and (2) patients with schizophrenia
Pokorny et al (2017)[125]	33		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo	
Middlefell (1967)[126]	36		Single-blind within-subjects crossover	"Psychiatric inpatients"	LSD	Sterile water injection placebo	No intervention
Griffiths et al (2006)[127]	36		Double-blind between subjects with within-subjects crossover	Healthy volunteers	Psilocybin	Methylphenidate	Volunteers were randomly assigned to receive either 2 sessions (random assignment) or 3 sessions (methylphenidate first 2 sessions and unblinded psilocybin on the third, these participants were not included in statistical analysis) to further obscure the study design
Schmidt et al (2013)[128]	42		Double-blind between subjects with within-subjects crossover	Healthy volunteers	Psilocybin	Placebo and ketamine	
Bowen et al (1970)[17]	44	2	Double-blind between subjects	"Inpatient alcoholics"	LSD	Low-dose LSD (25 µg)	
Pasquini et al (2020)[129]	50		Single-blind between subjects	Healthy volunteers	Ayahuasca	Placebo	
Denson and Sydiaha (1970)[130]	51		Unblinded between subjects	"Alcoholic" and "neurotic" patients	LSD	0	Waitlist control
Hollister et al (1969)[131]	52		Double-blind between subjects	"Alcoholic inpatients"	LSD	Dextroamphetamine 60 mg	
Griffiths et al (2016)[4]	56		Double-blind between subjects with within-subjects crossover	Life-threatening cancer diagnosis and *DSM-IV* diagnosis that included anxiety or depression symptoms	Psilocybin	Low-dose psilocybin	
Lewis et al (2017)[132]	58		Double-blind between subjects with within-subjects crossover	Healthy volunteers	Psilocybin	Placebo and different doses of psilocybin	
Mason et al (2020)[133]	60		Double-blind between subjects	Healthy volunteers	Psilocybin	Placebo	
Savage and McCabe (1973)[134]	78		Unblinded between subjects	"Paroled narcotic addicts"	LSD		Outpatient addiction program without LSD

(continued)

Table 1 (continued).

Publication	n	Experiment Number[b]	Study Design	Sample	Psychedelic	Drug Comparator	Non-Drug Comparator
Griffiths et al (2018)[135]	80		Double-blind between subjects	Healthy volunteers	Psilocybin	Very low dose psilocybin	Different degrees of support for spiritual practice
Johnson (1969)[18]	95		Single-blind between subjects	"Alcoholics"	LSD	Sodium amobarbital 3.75 g IV + methamphetamine 30 mg IV	Presence of therapist; routine outpatient care
Savage et al (1973)[15]	96		Double-blind between subjects	"Inpatients with a psychoneurotic diagnosis"	LSD	Low-dose LSD (50 µg)	Inpatient psychiatric treatment as usual
Tomsovic and Edwards (1970)[14]	97		Unblinded between subjects	"Alcoholics" treated in inpatient rehab (included "schizophrenics")	LSD		Treatment as usual (inpatient rehab)
Ditman et al (1969)[136]	99		Double-blind between subjects	"Inpatient alcoholics"	LSD	Methylphenidate and chlordiazepoxide	
Haertzen (1966)[137]	100		Single-blind within-subjects crossover	"Post-narcotic addicts"	LSD	Placebo, and different doses of LSD	Non-drug condition
Robinson et al (1963)[138]	101		Unblinded between subjects	Psychiatric inpatients with "psychoneurosis"	LSD	Hexobarbitone 0.1 g IV + methamphetamine 20 mg IV	Psychotherapy without drug
Kurland et al (1971)[20]	135		Double-blind between subjects	"Inpatient alcoholics"	LSD	High-dose (450 µg) vs low-dose (50 µg) LSD	
Rhead et al (1977)[19]	174		Unblinded between subjects	"Inpatient alcoholics"	DPT		Routine hospital treatment, routine hospital treatment with individualized psychotherapy
Ludwig et al (1969)[16]	176		Single-blind between subjects	"Inpatient alcoholics"	LSD		LSD with hypnosis and psychotherapy, LSD with psychotherapy alone, LSD alone and basic milieu therapy with equivalent time spent alone in the treatment room
Spitzer et al (1996)[139]	8		Double-blind within-subjects crossover	Healthy volunteers	Psilocybin	Placebo	

[a]Empty rows with gray cells entail the data in the article were derived from a parent study, which can be found in the first full row above the empty row. The language for the patient sample was taken directly from the articles themselves, without attempt to fit the language into modern nosologic categories. Quotes are used in several instances (eg, "alcoholics") because we are using the terms from the source but recognize some such terms may be considered stigmatizing in the present day.

[b]For articles that reported on more than one study, *experiment number* refers to different studies (experiments) within that article.

Abbreviations: 6-HDMT = 5-hydroxy-DMT, DMT = *N*,*N*-dimethyltryptamine, DPT = *N*,*N*-dipropyltryptamine, DXM = dextromethorphan, IM = intramuscular, IV = intravenous, LSD = lysergic acid diethylamide, MDE = 3,4-methylenedioxyethylamphetamine, MDMA = 3,4-methylenedioxymethamphetamine, SQ = subcutaneous.

Table 2. Active Non-Psychedelic Comparators Used in Randomized Psychedelic Trials

Active Control	n (%)
Amphetamine	8 (9.9)
Ketamine	3 (3.7)
Methamphetamine	3 (3.7)
Methylphenidate	3 (3.7)
Niacin	2 (2.5)
Chlordiazepoxide	2 (2.5)
Barbiturates	2 (2.5)
Ephedrine	1 (1.2)
MDE	1 (1.2)
Phenmetrazine	1 (1.2)
MDMA	1 (1.2)
Benactyzine	1 (1.2)
DXM	1 (1.2)
Sham ayahuasca[a]	1 (1.2)

[a]"The liquid used as placebo was designed to simulate organoleptic properties (taste and color) of ayahuasca, such as a bitter and sour taste, and a brownish color. It contained water, yeast, citric acid, zinc sulfate and caramel colorant. The presence of zinc sulfate also produced low to modest gastrointestinal distress..[59]

Abbreviations: DXM = dextromethorphan, MDE = 3,4-methylenedioxyethylamphetamine, MDMA = 3,4-methylenedioxymethamphetamine.

Control Conditions

Of 80 studies with a drug control condition, 49 (57.0%) used an inert placebo as a control, 16 (18.6%) used active comparators, 12 (14.0%) used both, and 3 (3.5%) used only different active psychedelic doses as a control.

Active Controls

Table 2 shows the list of active drug controls in blinded studies.

In addition, 7 studies used a low dose of the active psychedelic as an active placebo: 4 used low-dose psilocybin,[4,71,96,135] 2 used low-dose LSD,[17,102] and 1 used low-dose DMT.[52] Two LSD microdosing studies were not included in these calculations as microdoses are not intended to be subjectively psychoactive and are similar in strength to active placebo doses.

Eighteen studies used different active doses of the psychedelic under study as active comparators.

Pretreatment Controls

Six studies used some form of pretreatment to block psychedelic effects as a control (ie, comparison among multiple conditions in which the psychedelic is preceded by a manipulation or not).[24,30,67,70,103] Five of these used pretreatment with ketanserin (a 5-HT_{2A} antagonist) and placebo as a control for ketanserin prior to dosing with psilocybin, LSD, or ayahuasca.[24,30,67,103] The report by Vollenweider et al[24] of study 1 also used pretreatment with haloperidol or risperidone, in addition to ketanserin or placebo. Pokorny et al[70] did not use ketanserin, but rather pretreatment with buspirone, ergotamine, or placebo before psilocybin.

Non-Drug Controls

Fifteen studies used other non-drug controls. Of the 4 studies using within-subjects crossover designs, 2[126,137] used a no-intervention condition as a control; 1 used different combinations of LSD, hypnosis, and psychotherapy[57]; and the fourth[124] used a placebo-controlled within-subjects crossover and 2 separate no-intervention control groups. Of the 10 studies using a between-subjects design, 7 used a form of treatment as usual[14,15,18,19,121,134,138]; 1 used different combinations of LSD, hypnosis, and psychotherapy[16]; 1 used a waitlist control[130]; and 1, a study involving meditation, used different degrees of support for spiritual practice.[135]

A final study[127] used a between-subjects with within-subjects crossover design including a unique control design whereby participants were randomly assigned to either 2 or 3 sessions. If assigned to 2 sessions, participants received methylphenidate and psilocybin in random order. If assigned to 3, participants received 2 sessions of methylphenidate followed by unblinded psilocybin.[127]

Therapeutic Trials

A total of 21 studies had a goal to treat a defined medical condition, generally either related to a substance use disorder (SUD) or a non-SUD psychiatric condition or set of psychiatric symptoms. Twelve (57.1%) of these 21 studies included recruitment from inpatients and 1, from prisoners getting released on parole.[134]

Substance Use Disorder Studies

Using the terminology of SUD these studies, 10 treated "alcoholics,"[14,16–20,111,121,130,131] 1 treated "paroled narcotic addicts,"[134] and 1 treated "post-narcotic drug addict" inpatients.[57]

Non-SUD Psychiatric Disorder Studies

Three studies treated non-alcoholic, non-drug-related, non-psychotic psychiatric inpatients.[15,21,138] Four studies investigated slightly different aspects of anxiety or depression in serious medical illnesses,[4,5,101,102] 1 study treated OCD (obsessive-compulsive disorder),[96] and 1 treated treatment-resistant depression.[59]

Blinding

A total of 81 original studies were blinded, with 60 double-blinded and 21 single-blinded; 5 other studies were unblinded. Of the 81 blinded studies, 14 (17.3%) included some assessment of blind integrity. The form of blind integrity testing varied widely between studies (Table 3).

Monitor Effects

Of all 21 therapeutic studies, 2 (9.5%) assessed whether therapeutic effects differed between individual monitors,[5,16] and both found no such effects.

Reporting of Preparatory and Integration Sessions

Of 21 therapeutic studies, 10 noted the number of preparatory sessions and 10 noted the number of preparatory session hours. Only 5 studies reported the number of integration sessions or hours.

Table 3. Summary of Blind Integrity Assessments

Study	Participant Blind Assessed	Monitor Blind Assessed	Quantitative Reporting	Description
Bershad et al (2019)[87]	X		X	This was a study of LSD microdosing using doses of 6.5, 13, 26 µg and placebo. No subject correctly guessed they had received a hallucinogen in the 6.5-µg condition. During the 13-µg condition, 2/20 (10%) correctly guessed they had received a hallucinogen. In the 26-µg condition, 6/20 (30%) correctly guessed they had received a hallucinogen.
Carbonaro et al (2018)[85]	X		X	Participants received different doses of psilocybin, placebo, and DXM and were instructed they could receive a placebo or a range of 38 other psychoactive drugs. After each session, they completed a questionnaire, indicating which of 14 psychoactive drugs was most similar to their experience. 14/20 (70%) chose placebo after placebo. For psilocybin sessions, the majority correctly selected classic hallucinogen—17/20 (85%) at 10 mg/70 kg, 16/20 (80%) at 20 mg/70 kg, and 18/20 (90%) at 30 mg/70 kg. After 400 mg DXM, only 2/20 (10%) selected classic hallucinogen. All had previously taken classic hallucinogens and dissociative anesthetics.
Gasser et al (2014)[102]	X	X	X	Participants correctly guessed the dose of LSD (200 µg or 20 µg) administered in all 24 blinded sessions. Participants stated they were "very certain" about their guesses in 20/24 (83%) instances. Both therapists incorrectly guessed 20 µg as 200 µg once each, and were "very certain" in their guesses in 22/24 (92%) instances.
Griffiths et al (2006)[127]		X	X	This study used an instructional set in which participants and session monitors were informed they would receive 2 or 3 sessions, in at least one of which they would receive a moderate or high dose of psilocybin. They were informed they might also receive placebo or any of a list of 11 psychoactive drugs. They in fact each received high-dose psilocybin and methylphenidate. With these measures, 23% of sessions were misclassified by monitors—most often methylphenidate was classified as psilocybin. Measures of blind integrity were not collected from participants.
Griffiths et al (2011)[71]		X		This study used a range of psilocybin doses (5, 10, 20, and 30 mg/70 kg) administered in ascending or descending order, with placebo randomly interspersed. This dosing schedule was obscured from most staff. Although some staff who were blinded to drug condition on any given session were knowledgeable of the ascending vs descending design, other staff were blinded to this design, were assessed and unable to guess the dosing schedule. Measures of blind integrity were not collected from participants.
Griffiths et al (2016)[4]		X	X	Participants and monitors were told that participants would receive psilocybin in both sessions, ranging from a very low to high dose, with at least 1 moderate to high dose. In actual fact, a very low dose was received first following a high dose, or vice versa. 5/8 session monitors incorrectly guessed the study design. Monitors were also asked to guess the magnitude of drug dose administered on a visual analog scale. While ratings were significantly different between the high and low dose groups, there was some overlap in ratings.
Griffiths et al (2018)[135]		X	X	Participants and monitors were told that participants would receive psilocybin in every session, and that at least 1 session would involve a moderately high or high dose. All participants received at least 2 sessions and some received a third. The purpose of the third session was to help obscure the study design. None of the monitors was correctly able to guess the study design.
Grob et al (2011)[101]	X	X		This study did not quantify blind integrity testing, but stated "the drug order was almost always apparent to participants and investigators whether the treatment was psilocybin or placebo."
Palhano-Fontes et al (2019)[59]	X		X	This study utilized a sham ayahuasca placebo that looked and tasted like ayahuasca and induced nausea. In the study, 5/15 (33%) placebo recipients believed they had received ayahuasca. No ayahuasca participants believed they had received placebo. All were psychedelic naive and clinician-referred.
Ross et al (2016)[5]		X	X	Staff members correctly guessed the condition in 28/29 (97%) participants
Smart et al (1966)[121]	X	X	X	This study compared LSD 800 µg and ephedrine 60 mg in a between-participants design. Participants were not told which drug was being used. Moreover, "patients were unaware that two drugs were being used and they had no way of knowing which patients received lysergide. They were told that there is a great variation in how people react to the drug, that some react in a striking way and others only slightly." Therapists correctly guessed the drug in 19/20 (95%) of cases. In contrast, "in nearly every case" patients believed they received LSD ("Patients who got ephedrine interpreted it as a slight reaction to lysergide").
Soskin et al (1973)[21]		X	X	Therapists (not patients) were asked to guess the drug received. They guessed correctly 106/136 (78%) times. Broken down by drug condition, these were DPT: 51/72 (71%); Placebo: 55/64 (86%). Notably, DPT doses ranged from 15 mg to 30 mg and therapists were somewhat less successful in correctly identifying low dose (15–20 mg) DPT sessions.
Wikler et al (1965)[124]	X	NA (single-blind)		This study reported that participants "had previous experience with each of the drugs used (except in some cases, LSD-25), and were able to identify them by their effects on themselves (placebo was invariably reported as a 'blank')."
Holze et al, (2020)[26]	X		X	Participants correctly identified LSD 96% of the time (with 4% misidentifying it as MDMA), and placebo was correctly identified in all cases.

(continued)

Table 3 (continued).

Study	Participant Blind Assessed	Monitor Blind Assessed	Quantitative Reporting	Description
Holze et al (2021)[140,*]	X		X	"Generally, the 100 and 200 µg doses were identified as high doses, but these two doses could not be distinguished. The 25 µg dose of LSD was distinguished from placebo and identified correctly or as the 50 µg dose of LSD by most participants. Ketanserin and LSD together were identified correctly or mistaken as a low dose of LSD but never mistaken for a high dose of LSD."
Holze et al (2022)[141,*]	X		X	"Only one patient in the LSD-first group mistook LSD as placebo and realized that he had LSD the first time only when he received placebo during the second study phase."
Bogenschutz et al (2022)[142,*]	X	X	X	"Participants correctly guessed their treatment assignment in 93.6% of the first sessions, reporting a mean (SD) certainty of 88.5% (23.2%). In the second session, 94.7% guessed correctly, and mean (SD) certainty was 90.6% (21.5%). Study therapists correctly guessed treatment 92.4% of the time for first sessions and 97.4% for second sessions, and their mean (SD) certainties were 92.8% (16.3%) and 95.4% (2.9%), respectively."

*This study was published after the search time range of the systematic review.
Abbreviations: DXM = dextromethorphan, LSD = lysergic acid diethylamide, MDMA = 3,4-methylenedioxymethamphetamine.

DISCUSSION

General Design Considerations for Future Psychedelic Trials

Modern therapeutic psychedelic trials not only use drugs with distinct, recognizable subjective effects, but also generally involve high levels of interpersonal support. This is in part to minimize psychological distress,[143] but possibly also an assumption that extensive psychological support is therapeutically necessary. Thus, modern psychedelic therapy trials are effectively drug-plus-psychotherapy trials. This complicates discussion of blinding and what an adequate control condition for psychedelic therapy trials might be.

Active Versus Inert Placebos

Inert placebo controlled psychedelic trials have been criticized for being effectively unblinded.[9] Active controls, employed in 32.6% of studies here, have been suggested as a remedy to improve blinding. However, it remains unclear the extent to which an active placebo can cause participants to believe they have received the active drug. In modern trials, the trial by Palhano-Fontes et al[59] performed best, with 33% of placebo participants (who received a taste and appearance matched placebo; Table 3) believing they had received ayahuasca. Notably, all were clinician referred and psychedelic-naive. In the one study that used dextromethorphan (400 mg/70 kg) as an active comparator,[85] only 10% of participants mistook it for a classic hallucinogen, though these were psychedelic- and dissociative-experienced participants. Interestingly, a similar study by the same group[144] tested different doses of dextromethorphan versus a benzodiazepine in psychedelic-experienced individuals, and 92% of subjects that received 400 mg dextromethorphan believed they had received a classic psychedelic. These were both within-subject crossover studies. In the former study, the contrast between dextromethorphan and genuine psilocybin may have reduced identification of dextromethorphan as a classic psychedelic. In the latter, the lack of this contrast, and a likely expectation of receiving psilocybin (at the time this group was becoming well known for psilocybin research), may have increased identification of dextromethorphan as a classic psychedelic. These marked differences highlight that successful blinding is unlikely to be a simple function of the active comparator's effects, but also must take into account the expectations surrounding them.

An additional concern for therapeutic studies is that some active comparators may have therapeutic effects, which would impair the trial's ability to determine efficacy. For example, dextromethorphan is an *N*-methyl-D-aspartate (NMDA) antagonist, like ketamine, which is known to have efficacy for treating depression. If dextromethorphan had a therapeutic effect, its utility as a control would be diminished.

Although Smart et al[121] report achieving successful patient blinding with ephedrine "in nearly every case," this likely had much to do with psychedelic naivete and deception (patients were told only that a single new drug was being studied), and, as mentioned by the study authors, many patients were convinced they received LSD due to substantial media coverage of LSD at the time. Monitors, however, correctly identified assignment condition in 95% of cases.

Other drugs, such as oral tetrahydrocannabinol (THC), that may be good active placebo candidates deserve study and have not yet been used. Appropriate active controls and their dosages should be selected so as to not pose undue risks that may limit participant selection—ephedrine and other amphetamine-like compounds, for example, have significant cardiovascular effects at higher doses that likely increase risks compared to classic psychedelics. Ultimately, how well active placebos can mask assignment condition is an empirical question that will rely upon formal assessment. An effective option for an active control may be a low-dose control of the active drug, or a range of doses, as was recently performed in a phase 2 trial of psilocybin (25 vs 10 vs 1 mg) for treatment-resistant depression.[145] Although uncommon, this is an acceptable control condition for trials leading to US Food and Drug Administration (FDA) approval (21 CFR 314.126[b][2]). It allows for demonstration of dose-response effects. A very low dose of an active drug that is not expected to be psychoactive could help minimize expectancy effects by making it possible to tell all participants they

will receive the psychedelic drug. Using a higher dose that is likely to have subjective effects would better improve blinding and control for expectancy effects, though at the risk of introducing genuine therapeutic effects. We applaud the design of the EPIsoDE trial for treatment-resistant depression (NCT04670081) being conducted in Germany, which uses 3 conditions: psilocybin 25 mg, psilocybin 5 mg, and a nicotinic acid placebo. However, placebo control conditions are useful for safety, not just efficacy purposes. The use of active controls is useful for clarifying efficacy, but adverse events and side effect assessments can be better determined with a true placebo control condition.

Non-Drug Controls

The 15 studies using non-drug controls included treatment as usual, a no-intervention condition, waitlist control, and different psychosocial interventions (such as psychotherapies, hypnosis, and varying degrees of psychological or spiritual support). Although non-drug controls are appropriate to control the non-drug elements of psychedelic therapy that are independent of drug effects, they present many problems. Blinding is difficult or impossible for non-drug controls, and waitlist controls may act as nocebo conditions.[146] Moreover, non-drug controls do not control for effects of the interaction of drug and non-drug therapeutic elements such as psychotherapy. However, few studies claim that psychedelics are therapeutic without this interaction, but if demonstrating this is a specific interest then studies with minimal psychotherapeutic controls, or in anesthetized patients, could be attempted.[10] Such a study is being performed with ketamine versus saline in depressed patients undergoing surgery with general anesthesia (NCT03861988).

Three older LSD studies included minimal psychological support controls.[16,18,57] In the study by Ludwig et al,[16] all subjects received a single 2-hour preparatory session, and one group received LSD with minimal support—"Once the session began, therapists were not to engage in any dialogue with patients except for offering them brief support if patients began to appear anxious or panicky."(p61) In the study by Ludwig and Levine,[57] one group also received LSD with minimal support, though this session was preceded by meetings with a therapist. In the report by Johnson,[18] patients in one group were alone with a nurse who "gave supportive nursing care but minimized verbal interaction while they were under the effects of LSD."(p64) In these 3 studies, comparison groups with therapeutic support involved a great deal of talking with a therapist during the drug session, which is atypical in modern trials. Although no modern trials tested minimal psychological support controls, this may be feasible (at the risk of increasing psychological distress).

Blinding Success and Assessment

Only 17.3% of blinded studies included some form of blind integrity assessment. In general, these studies had poor success in maintaining the blind. Some of these assessed blinding only of monitors, rather than patients. Inasmuch as studies are intended to be "double-blind," blind assessment should be performed with both monitors and participants. We are aware of 3 more randomized studies that have been published after the search that tested blind integrity. In a study of 2 doses of psilocybin versus 2 doses of niacin for *DSM-IV* alcohol dependence,[142] 94% of participants correctly guessed their assignment after the first dosing session and reported a mean 89% certainty, while therapists similarly guessed correctly 92% of the time with 93% certainty. Another study[140] compared a range of LSD doses. After the drug session, participants misidentified LSD 25 µg as placebo 6% of the time, though never misidentified LSD 50, 100, or 200 µg as placebo. Finally, a study that tested 2 doses of LSD 200 µg versus placebo for anxiety[141] found that only 1 of 19 patients who received LSD believed they had received placebo.

The extent to which unblinding in psychedelic trials compares to unblinding in psychiatric trials generally is unclear. Indeed, although functional unblinding may be common in psychoactive drug trials generally,[9,147–152] blind assessment is not. In a review of 94 psychiatric trials,[153] only 8 reported assessment of blinding and 5 reported quantitative assessments in patients. Similarly, Muthukumaraswamy et al[9] examined randomized controlled trials of ketamine for depressive disorders and found that of 30, only 5 assessed masking in any way and only 1[154] was successful. This latter study was a parallel-groups trial in which 55% of both ketamine and midazolam groups correctly guessed their assignment.

The fact that a majority of participants (53.8% of participants in trials that reported this) had prior experience with psychedelics could also significantly impact blinding. Studies that exclude psychedelic-experienced participants could minimize this.

To summarize, we second Muthukumaraswamy et al[9] in arguing for routine assessment of blinding and agree this should be done soon after the dosing session to minimize unblinding due to efficacy. This would also facilitate analysis of factors predictive of blind maintenance (for example, psychedelic naivete or particular referral sources) to improve future attempts. In addition, the field as a whole should attempt to arrive at a consensus of what adequate blinding would actually be. Active psychedelics are likely to be recognized as such, so successful blinding would probably entail a high proportion of all participants (active drug and control) believing they had received the active drug rather than both groups guessing at chance levels.

Monitor Effects

The general psychotherapy literature suggests that some therapists are more effective than others and that this effectiveness may differ by patient racial/ethnic group.[155,156] The only two studies here that assessed monitor effects found none.[5,16] If some monitors are systematically better than others, then trials might benefit from balancing monitor assignment between participants, or at least statistically

accounting for monitor effects. Clarifying whether monitor effects exist in future studies would be useful to determine whether this would be necessary.

Limitations

Limitations in this review largely arise from limitations of the studies themselves. For example, a minority of blinded studies reported blind integrity assessment, which limits conclusions about blind testing efficacy and which strategies may maximize success. Participant characteristics, including prior psychedelic use and race, were also inconsistently reported. Studies did not always define which drugs were considered psychedelics. Non-drug controls were not always described in sufficient detail, and heterogeneity of study designs limits some general overview conclusions. As this review is focused on methods, we did not examine questions of efficacy. It is also possible that we have missed randomized studies that would have met inclusion criteria.

Beyond Blinded Trials

A successfully blinded trial equally distributes expectancy effects (placebo effects) between the active and control arms. At the hypothetical extreme, if blinding is impossible, then "blinding" a trial adds no further information. Under this scenario, it is preferable to perform other types of trials, such as unblinded comparative efficacy studies with a consistently efficacious comparator. Although blinding is not truly impossible (some participants are successfully masked, and it is possible this proportion could be increased), unblinded comparative efficacy trials are useful in proportion to how much blinding fails. While it is difficult to know the extent to which unblinding drives differential group effects, it is informative to compare placebo effects in relatively unblinded psychedelic studies to those of relatively blinded non-psychedelic studies. For example, the average effect size of placebo effect in treatment resistant depression is $d = 1.1$.[157] However, in the study by Palhano-Fontes et al,[59] the placebo effect is only $d = 0.5$, and this may be due to unblinding leading to a differential placebo effect.

Unblinded trials risk being driven by expectancies of benefit. Thus, it would be prudent to measure these therapeutic expectancies. This could be accomplished with the Credibility/Expectancy Questionnaire (CEQ)[158] or a bespoke measure for psychedelic trials. It would be instructive to know the extent to which such a measure predicts treatment effects, and it could be included as a control variable for estimating treatment effects.

There is one ongoing comparative efficacy trial of open label psilocybin versus nicotine replacement for smoking cessation (NCT01943994). Carhart-Harris et al[2] performed a double-blinded trial with features of a comparative efficacy trial. It utilized a double-dummy design in which participants received escitalopram or placebo and received a dosing session with psilocybin or placebo. Blind efficacy was not reported.

Examining more severely clinically impaired patients might minimize placebo effects. For example, an unblinded, randomized trial comparing electroconvulsive therapy (ECT), a highly effective treatment, to psilocybin in treatment-resistant depression would provide evidence consistent with the efficacy of psilocybin despite a lack of placebo or blinding. This could be performed as a non-inferiority trial, similar to the ELEKT-D study comparing open-label IV ketamine to ECT.[159]

Recommendations

Based on this review, the following recommendations can be made:

1. Assess blinding belief, certainty, and reasoning for guesses among patients and monitors. Ideally, perform this the same day as a treatment session, after effects have largely worn off. Optimal blinding will likely entail equivalent numbers in the control group believing they received the active drug. However, blinding has value even if outcomes fall short of this standard, as greater blinding interferes with the ability of placebo/expectancy effects to drive results.[160]
2. Perform dose response trials using a range of active doses. Notably, the FDA is able to use such trials in support of approval, even without a placebo (21 CFR 314.126[b][2]).
3. Measure therapeutic expectancies. This could be performed with the Credibility/Expectancy Questionnaire (CEQ)[158] or a bespoke psychedelic-specific expectancy measure.
4. Use active placebos (such as oral THC) that may increase the likelihood of successful blinding.
5. Perform open-label pragmatic and comparative efficacy trials to complement blinded placebo-controlled studies. Comprehensive conclusions are ultimately drawn from evaluations across a variety of study designs, and both study designs offer complementary advantages and disadvantages.
6. Consider comparing the full complement of typical psychedelic therapy (preparation, support during dosing, integration) to a minimally supportive drug condition lacking those elements. This may be infeasible due to increased risk of distress, but would elucidate the utility of therapeutic support and the numbers and types of sessions necessary. A low threshold to abort the experience due to distress with a 5-HT_{2A} antagonist like risperidone might mitigate ethical concerns regarding psychological distress.
7. Especially for therapeutic trials, consider recruiting psychedelic-naive and clinician referred patients. This may aid blinding and reduce expectancy effects.

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REFERENCES

1. Davis AK, Barrett FS, May DG, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA Psychiatry*. 2021;78(5):481–489.
2. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of psilocybin versus escitalopram for depression. *N Engl J Med*. 2021;384(15):1402–1411.
3. Johnson MW, Garcia-Romeu A, Cosimano MP, et al. Pilot study of the 5-HT_{2A}R agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol*. 2014;28(11):983–992.
4. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol*. 2016;30(12):1181–1197.
5. Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol*. 2016;30(12):1165–1180.
6. Bogenschutz MP, Forcehimes AA, Pommy JA, et al. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *J Psychopharmacol*. 2015;29(3):289–299.
7. Schindler EAD, Sewell RA, Gottschalk CH, et al. Exploratory controlled study of the migraine-suppressing effects of psilocybin. *Neurotherapeutics*. 2021;18(1):534–543.
8. Aday JS, Heifets BD, Pratscher SD, et al. Great Expectations: recommendations for improving the methodological rigor of psychedelic clinical trials. *Psychopharmacology (Berl)*. 2022;239(6):1989–2010.
9. Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. *Expert Rev Clin Pharmacol*. 2021;14(ja):1133–1152.
10. Yaden DB, Griffiths RR. The subjective effects of psychedelics are necessary for their enduring therapeutic effects. *ACS Pharmacol Transl Sci*. 2020;4(2):568–572.
11. Nayak S, Johnson MW. Psychedelics and psychotherapy. *Pharmacopsychiatry*. 2021;54(4):167–175.
12. Gukasyan N, Nayak SM. Psychedelics, placebo effects, and set and setting: insights from common factors theory of psychotherapy. *Transcult Psychiatry*. 2021;59(5):652-664.
13. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
14. Tomsovic M, Edwards RV. Lysergide treatment of schizophrenic and nonschizophrenic alcoholics: a controlled evaluation. *Q J Stud Alcohol*. 1970;31(4):932–949.
15. Savage C, Cabe OLM, Kurland AA, et al.. *LSD-Assisted Psychotherapy in the Treatment of Severe Chronic Neurosis*. Farmingdale, NY: Baywood Pub Co; 1973.
16. Ludwig A, Levine J, Stark L, et al. A clinical study of LSD treatment in alcoholism. *Am J Psychiatry*. 1969;126(1):59–69.
17. Bowen WT, Soskin RA, Chotlos JW. Lysergic acid diethylamide as a variable in the hospital treatment of alcoholism: a follow-up study. *J Nerv Ment Dis*. 1970;150(2):111–118.
18. Johnson FG. LSD in the treatment of alcoholism. *Am J Psychiatry*. 1969;126(4):481–487.
19. Rhead J, Soskin R, Turek I. Psychedelic drug (DPT)-assisted psychotherapy with alcoholics: a controlled study. *J Psychoactive Drugs*. 1977;9(4):287–300.
20. Kurland A, Savage C, Pahnke WN, et al. LSD in the treatment of alcoholics. *Pharmacopsychiatry*. 1971;4(02):83–94.
21. Soskin RA. The use of LSD in time-limited psychotherapy. *J Nerv Ment Dis*. 1973;157(6):410–419.
22. Haertzen CA. On the addiction research center inventory scores of former addicts receiving LSD and untreated schizophrenics. *Psychol Rep*. 1964;14(2):483–488.
23. Isbell H, Logan CR. Studies on the diethylamide of lysergic acid (LSD-25), II: effects of chlorpromazine, azacyclonol, and reserpine on the intensity of the LSD-reaction. *AMA Arch Neurol Psychiatry*. 1957;77(4):350–358.
24. Vollenweider FX, Vollenweider-Scherpenhuyzen MFI, Bäbler A, et al. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport*. 1998;9(17):3897–3902.
25. Hollister LE, Degan RO, Schultz SD. An experimental approach to facilitation of psychotherapy by psychotomimetic drugs. *J Ment Sci*. 1962;108(452):99–100.
26. Holze F, Vizeli P, Müller F, et al. Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects. *Neuropsychopharmacology*. 2020;45(3):462–471.
27. Holze F, Duthaler U, Vizeli P, et al. Pharmacokinetics and subjective effects of a novel oral LSD formulation in healthy subjects. *Br J Clin Pharmacol*. 2019;85(7):1474–1483.
28. Wittmann M, Carter O, Hasler F, et al. Effects of psilocybin on time perception and temporal control of behaviour in humans. *J Psychopharmacol*. 2007;21(1):50–64.
29. Wackermann J, Wittmann M, Hasler F, et al. Effects of varied doses of psilocybin on time interval reproduction in human subjects. *Neurosci Lett*. 2008;435(1):51–55.
30. Preller KH, Herdener M, Pokorny T, et al. The fabric of meaning and subjective effects in LSD-induced states depend on serotonin 2A receptor activation. *Curr Biol*. 2017;27(3):451–457.
31. Kraehenmann R, Pokorny D, Aicher H, et al. LSD increases primary process thinking via serotonin 2A receptor activation. *Front Pharmacol*. 2017;8:814.
32. Kraehenmann R, Pokorny D, Vollenweider L, et al. Dreamlike effects of LSD on waking imagery in humans depend on serotonin 2A receptor activation. *Psychopharmacology (Berl)*. 2017;234(13):2031–2046.
33. Preller KH, Schilbach L, Pokorny T, et al. Role of the 5-HT_{2A} receptor in self-and other-initiated social interaction in lysergic acid diethylamide-induced states: a pharmacological fMRI study. *J Neurosci*. 2018;38(14):3603–3611.
34. Preller KH, Burt JB, Ji JL, et al. Changes in global and thalamic brain connectivity in lsd-induced altered states of consciousness are attributable to the 5-HT2A receptor. Hunt LT, Behrens TE, eds. eLife. 2018;7:e35082.
35. Barrett FS, Preller KH, Herdener M, et al. Serotonin 2A receptor signaling underlies LSD-induced alteration of the neural response

to dynamic changes in music. *Cerebral Cortex*. 2018;28(11):3939–3950.
36. Preller KH, Razi A, Zeidman P, et al. Effective connectivity changes in LSD-induced altered states of consciousness in humans. *Proc Natl Acad Sci U S A*. 2019;116(7):2743–2748.
37. Pokorny T, Duerler P, Seifritz E, et al. LSD acutely impairs working memory, executive functions, and cognitive flexibility, but not risk-based decision-making. *Psychol Med*. 2020;50(13):2255–2264.
38. Jaffe J, Dahlberg CC, Luria J, et al. Speech rhythms in patient monologues: the influence of LSD-25 and dextroamphetamine. *Biol Psychiatry*. 1972;4(3):243–246.
39. Jaffe J, Dahlberg CC, Luria J, et al. Effects of LSD-25 and dextroamphetamine on speech rhythms in psychotherapy dialogues. *Biol Psychiatry*. 1973;6(1):93–96.
40. Dahlberg CC, Jaffe J. The effects of LSD-25 and dextroamphetamine on the use of defensive language. *J Clin Psychol*. 1979;35(2):250–254.
41. Natale M, Dahlberg CC, Jaffe J. The effect of psychotomimetics on therapist–patient matching of speech "rhythms". *J Commun Disord*. 1979;12(1):45–52.
42. Mueller F, Lenz C, Dolder PC, et al. Acute effects of LSD on amygdala activity during processing of fearful stimuli in healthy subjects. *Transl Psychiatry*. 2017;7(4):e1084.
43. Dolder PC, Schmid Y, Müller F, et al. LSD acutely impairs fear recognition and enhances emotional empathy and sociality. *Neuropsychopharmacology*. 2016;41(11):2638–2646.
44. Liechti ME, Dolder PC, Schmid Y. Alterations of consciousness and mystical-type experiences after acute LSD in humans. *Psychopharmacology (Berl)*. 2017;234(9-10):1499–1510.
45. Dolder PC, Grünblatt E, Müller F, et al. A single dose of LSD does not alter gene expression of the serotonin 2a receptor gene (HTR2A) or early growth response genes (EGR1-3) in healthy subjects. *Front Pharmacol*. 2017;8:423.
46. Müller F, Lenz C, Dolder P, et al. Increased thalamic resting-state connectivity as a core driver of LSD-induced hallucinations. *Acta Psychiatr Scand*. 2017;136(6):648–657.
47. Müller F, Dolder PC, Schmidt A, et al. Altered network hub connectivity after acute LSD administration. *Neuroimage Clin*. 2018;18:694–701.
48. Schmidt A, Müller F, Lenz C, et al. Acute LSD effects on response inhibition neural networks. *Psychol Med*. 2018;48(9):1464–1473.
49. Schmid Y, Enzler F, Gasser P, et al. Acute effects of lysergic acid diethylamide in healthy subjects. *Biol Psychiatry*. 2015;78(8):544–553.
50. Strajhar P, Schmid Y, Liakoni E, et al. Acute effects of lysergic acid diethylamide on circulating steroid levels in healthy subjects. *J Neuroendocrinol*. 2016;28(3):12374.
51. Schmid Y, Liechti ME. Long-lasting subjective effects of LSD in normal subjects. *Psychopharmacology (Berl)*. 2018;235(2):535–545.
52. Strassman RJ, Qualls CR. Dose-response study of N,N-dimethyltryptamine in humans, I: neuroendocrine, autonomic, and cardiovascular effects. *Arch Gen Psychiatry*. 1994;51(2):85–97.
53. Strassman RJ, Qualls CR, Uhlenhuth EH, et al. Dose-response study of N,N-dimethyltryptamine in humans, II: subjective effects and preliminary results of a new rating scale. *Arch Gen Psychiatry*. 1994;51(2):98–108.
54. Riba J, Valle M, Urbano G, et al. Human pharmacology of ayahuasca: subjective and cardiovascular effects, monoamine metabolite excretion, and pharmacokinetics. *J Pharmacol Exp Ther*. 2003;306(1):73–83.
55. Riba J, Anderer P, Morte A, et al. Topographic pharmaco-EEG mapping of the effects of the South American psychoactive beverage ayahuasca in healthy volunteers. *Br J Clin Pharmacol*. 2002;53(6):613–628.
56. Riba J, Rodríguez-Fornells A, Barbanoj MJ. Effects of ayahuasca on sensory and sensorimotor gating in humans as measured by P50 suppression and prepulse inhibition of the startle reflex, respectively. *Psychopharmacology (Berl)*. 2002;165(1):18–28.
57. Ludwig AM, Levine J. A controlled comparison of five brief treatment techniques employing LSD, hypnosis, and psychotherapy. *Am J Psychother*. 1965;19(3):417–435.
58. Levine J, Ludwig AM. Alterations in consciousness produced by combinations of LSD, hypnosis and psychotherapy. *Psychopharmacology (Berl)*. 1965;7(2):123–137.
59. Palhano-Fontes F, Barreto D, Onias H, et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychol Med*. 2019;49(4):655–663.
60. Zeifman RJ, Palhano-Fontes F, Hallak J, et al. The impact of ayahuasca on suicidality: results from a randomized controlled trial. *Front Pharmacol*. 2019;10:1325.
61. Galvão ACde M, de Almeida RN, Silva EADS, et al. Cortisol modulation by ayahuasca in patients with treatment resistant depression and healthy controls. *Front Psychiatry*. 2018;9:185.
62. de Almeida RN, GalvãoACde M, da Silva FS, et al. Modulation of serum brain-derived neurotrophic factor by a single dose of ayahuasca: Observation from a randomized controlled trial. *Front Psychol*. 2019;10:1234.
63. Smigielski L, Kometer M, Scheidegger M, et al. Characterization and prediction of acute and sustained response to psychedelic psilocybin in a mindfulness group retreat. *Sci Rep*. 2019;9(1):14914.
64. Smigielski L, Scheidegger M, Kometer M, et al. Psilocybin-assisted mindfulness training modulates self-consciousness and brain default mode network connectivity with lasting effects. *Neuroimage*. 2019;196:207–215.
65. Yanakieva S, Polychroni N, Family N, et al. The effects of microdose LSD on time perception: a randomised, double-blind, placebo-controlled trial. *Psychopharmacology (Berl)*. 2019;236(4):1159–1170.
66. Family N, Maillet EL, Williams LTJ, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of low dose lysergic acid diethylamide (LSD) in healthy older volunteers. *Psychopharmacology (Berl)*. 2020;237(3):841–853.
67. Kometer M, Schmidt A, Bachmann R, et al. Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. *Biol Psychiatry*. 2012;72(11):898–906.
68. Kometer M, Schmidt A, Jäncke L, et al. Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α oscillations, N170 visual-evoked potentials, and visual hallucinations. *J Neurosci*. 2013;33(25):10544–10551.
69. Kometer M, Pokorny T, Seifritz E, et al. Psilocybin-induced spiritual experiences and insightfulness are associated with synchronization of neuronal oscillations. *Psychopharmacology (Berl)*. 2015;232(19):3663–3676.
70. Pokorny T, Preller KH, Kraehenmann R, et al. Modulatory effect of the 5-HT1A agonist buspirone and the mixed non-hallucinogenic 5-HT1A/2A agonist ergotamine on psilocybin-induced psychedelic experience. *Eur Neuropsychopharmacol*. 2016;26(4):756–766.
71. Griffiths RR, Johnson MW, Richards WA, et al. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology (Berl)*. 2011;218(4):649–665.
72. Johnson MW, Sewell RA, Griffiths RR. Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers. *Drug Alcohol Depend*. 2012;123(1-3):132–140.
73. Gouzoulis-Mayfrank E, Heekeren K, Neukirch A, et al. Psychological effects of (S)-ketamine and N,N-dimethyltryptamine (DMT): a double-blind, cross-over study in healthy volunteers. *Pharmacopsychiatry*. 2005;38(6):301–311.
74. Gouzoulis-Mayfrank E, Heekeren K, Neukirch A, et al. Inhibition of return in the human 5HT2A agonist and NMDA antagonist model of psychosis. *Neuropsychopharmacology*. 2006;31(2):431–441.
75. Heekeren K, Neukirch A, Daumann J, et al. Prepulse inhibition of the startle reflex and its attentional modulation in the human S-ketamine and N,N-dimethyltryptamine (DMT) models of psychosis. *J Psychopharmacol*. 2007;21(3):312–320.
76. Heekeren K, Daumann J, Neukirch A, et al. Mismatch negativity generation in the human 5HT2A agonist and NMDA antagonist model of psychosis. *Psychopharmacology (Berl)*. 2008;199(1):77–88.
77. Gouzoulis-Mayfrank E, Thelen B, Habermeyer E, et al. Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and d -methamphetamine in healthy volunteers. *Psychopharmacology (Berl)*. 1999;142(1):41–50.
78. Gouzoulis-Mayfrank E, Heekeren K, Thelen B, et al. Effects of the hallucinogen psilocybin on habituation and prepulse inhibition of the startle reflex in humans. *Behav Pharmacol*. 1998;9(7):561–566.
79. Gouzoulis-Mayfrank E, Schreckenberger M, Sabri O, et al. Neurometabolic effects of psilocybin, 3,4-methylenedioxyethylamphetamine (MDE) and d-methamphetamine in healthy volunteers: a double-blind, placebo-controlled PET study with [18F]FDG. *Neuropsychopharmacology*. 1999;20(6):565–581.
80. Gouzoulis-Mayfrank E, Thelen B, Maier S, et al. Effects of the hallucinogen psilocybin on covert orienting of visual attention in humans. *Neuropsychobiology*. 2002;45(4):205–212.
81. Kraehenmann R, Preller KH, Scheidegger M, et al. Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. *Biol Psychiatry*. 2015;78(8):572–581.
82. Grimm O, Kraehenmann R, Preller KH, et al. Psilocybin modulates functional connectivity of the amygdala during emotional face discrimination. *Eur Neuropsychopharmacol*. 2018;28(6):691–700.
83. Daumann J, Heekeren K, Neukirch A, et al. Pharmacological modulation of the neural basis underlying inhibition of return (IOR) in the human 5-HT2A agonist and NMDA antagonist model of psychosis. *Psychopharmacology (Berl)*. 2008;200(4):573–583.
84. Daumann J, Wagner D, Heekeren K, et al. Neuronal correlates of visual and auditory alertness in the DMT and ketamine model of

psychosis. *J Psychopharmacol*. 2010;24(10):1515–1524.
85. Carbonaro TM, Johnson MW, Hurwitz E, et al. Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: similarities and differences in subjective experiences. *Psychopharmacology (Berl)*. 2018;235(2):521–534.
86. Barrett FS, Carbonaro TM, Hurwitz E, et al. Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: effects on cognition. *Psychopharmacology (Berl)*. 2018;235(10):2915–2927.
87. Bershad AK, Schepers ST, Bremmer MP, et al. Acute subjective and behavioral effects of microdoses of lysergic acid diethylamide in healthy human volunteers. *Biol Psychiatry*. 2019;86(10):792–800.
88. Bershad AK, Preller KH, Lee R, et al. Preliminary report on the effects of a low dose of LSD on resting-state amygdala functional connectivity. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2020;5(4):461–467.
89. Natale M, Kowitt M, Dahlberg CC, et al. Effect of psychotomimetics (LSD and dextroamphetamine) on the use of figurative language during psychoanalysis. *J Consult Clin Psychol*. 1978;46(6):1579–1580.
90. Rosenberg DE, Isbell H, Miner EJ, et al. The effect of N,N-dimethyltryptamine in human subjects tolerant to lysergic acid diethylamide. *Psychopharmacology (Berl)*. 1964;5(3):217–227.
91. Vollenweider FX, Vontobel P, Hell D, et al. 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in man–a PET study with [11C]raclopride. *Neuropsychopharmacology*. 1999;20(5):424–433.
92. Netz B, Jonsson CO, Bergqvist S. Effects of lysergic acid diethylamide (LSD-25) on normal subjects in a schizophrenia-discriminating test battery. *Scand J Psychol*. 1963;4(1):143–148.
93. Dolezal V, Hausner M. Comparative phenomenology of experimental mental alterations after application of LSD, benactyzine and phenmetrzine. *Act Nerv Super (Praha)*. 1968;10(3):280–282.
94. Hasler F, Grimberg U, Benz MA, et al. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. *Psychopharmacology (Berl)*. 2004;172(2):145–156.
95. Carter OL, Burr DC, Pettigrew JD, et al. Using psilocybin to investigate the relationship between attention, working memory, and the serotonin 1A and 2A receptors. *J Cogn Neurosci*. 2005;17(10):1497–1508.
96. Moreno FA, Wiegand CB, Taitano EK, et al. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *J Clin Psychiatry*. 2006;67(11):1735–1740.
97. Santos RG, Landeira-Fernandez J, Strassman RJ, et al. Effects of ayahuasca on psychometric measures of anxiety, panic-like and hopelessness in Santo Daime members. *J Ethnopharmacol*. 2007;112(3):507–513.
98. Dos Santos RG, Valle M, Bouso JC, et al. Autonomic, neuroendocrine, and immunological effects of ayahuasca: a comparative study with d-amphetamine. *J Clin Psychopharmacol*. 2011;31(6):717–726.
99. Alonso JF, Romero S, Mañanas MÀ, et al. Serotonergic psychedelics temporarily modify information transfer in humans. *Int J Neuropsychopharmacol*. 2015;18(8):pyv039.
100. Carter OL, Pettigrew JD, Hasler F, et al. Modulating the rate and rhythmicity of perceptual rivalry alternations with the mixed 5-HT2A and 5-HT1A agonist psilocybin. *Neuropsychopharmacology*. 2005;30(6):1154–1162.
101. Grob CS, Danforth AL, Chopra GS, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry*. 2011;68(1):71–78.
102. Gasser P, Holstein D, Michel Y, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *J Nerv Ment Dis*. 2014;202(7):513–520.
103. Valle M, Maqueda AE, Rabella M, et al. Inhibition of alpha oscillations through serotonin-2A receptor activation underlies the visual effects of ayahuasca in humans. *Eur Neuropsychopharmacol*. 2016;26(7):1161–1175.
104. Strassman RJ, Qualls CR, Berg LM. Differential tolerance to biological and subjective effects of four closely spaced doses of N,N-dimethyltryptamine in humans. *Biol Psychiatry*. 1996;39(9):784–795.
105. Riba J, Romero S, Grasa E, et al. Increased frontal and paralimbic activation following ayahuasca, the pan-Amazonian inebriant. *Psychopharmacology (Berl)*. 2006;186(1):93–98.
106. Carhart-Harris RL, Leech R, Williams TM, et al. Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin. *Br J Psychiatry*. 2012;200(3):238–244.
107. Vollenweider FX, Csomor PA, Knappe B, et al. The effects of the preferential 5-HT2A agonist psilocybin on prepulse inhibition of startle in healthy human volunteers depend on interstimulus interval. *Neuropsychopharmacology*. 2007;32(9):1876–1887.
108. Quednow BB, Kometer M, Geyer MA, et al. Psilocybin-induced deficits in automatic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. *Neuropsychopharmacology*. 2012;37(3):630–640.
109. Kometer M, Cahn BR, Andel D, et al. The 5-HT2A/1A agonist psilocybin disrupts modal object completion associated with visual hallucinations. *Biol Psychiatry*. 2011;69(5):399–406.
110. Dos Santos RG, Grasa E, Valle M, et al. Pharmacology of ayahuasca administered in two repeated doses. *Psychopharmacology (Berl)*. 2012;219(4):1039–1053.
111. Soskin RA, Grof S, Richards WA. Low doses of dipropyltryptamine in psychotherapy. *Arch Gen Psychiatry*. 1973;28(6):817–821.
112. Umbricht D, Vollenweider FX, Schmid L, et al. Effects of the 5-HT2A agonist psilocybin on mismatch negativity generation and AX-continuous performance task: implications for the neuropharmacology of cognitive deficits in schizophrenia. *Neuropsychopharmacology*. 2003;28(1):170–181.
113. Riba J, Anderer P, Jané F, et al. Effects of the South American psychoactive beverage ayahuasca on regional brain electrical activity in humans: a functional neuroimaging study using low-resolution electromagnetic tomography. *Neuropsychobiology*. 2004;50(1):89–101.
114. Tagliazucchi E, Roseman L, Kaelen M, et al. Increased global functional connectivity correlates with LSD-induced ego dissolution. *Curr Biol*. 2016;26(8):1043–1050.
115. Speth J, Speth C, Kaelen M, et al. Decreased mental time travel to the past correlates with default-mode network disintegration under lysergic acid diethylamide. *J Psychopharmacol*. 2016;30(4):344–353.
116. Timmermann C, Spriggs MJ, Kaelen M, et al. LSD modulates effective connectivity and neural adaptation mechanisms in an auditory oddball paradigm. *Neuropharmacology*. 2018;142:251–262.
117. Bravermanová A, Viktorinová M, Tylš F, et al. Psilocybin disrupts sensory and higher order cognitive processing but not pre-attentive cognitive processing-study on P300 and mismatch negativity in healthy volunteers. *Psychopharmacology (Berl)*. 2018;235(2):491–503.
118. Barbanoj MJ, Riba J, Clos S, et al. Daytime ayahuasca administration modulates REM and slow-wave sleep in healthy volunteers. *Psychopharmacology (Berl)*. 2008;196(2):315–326.
119. Preller KH, Duerler P, Burt JB, et al. Psilocybin induces time-dependent changes in global functional connectivity. *Biol Psychiatry*. 2020;88(2):197–207.
120. Preller KH, Pokorny T, Hock A, et al. Effects of serotonin 2A/1A receptor stimulation on social exclusion processing. *Proc Natl Acad Sci U S A*. 2016;113(18):5119–5124.
121. Smart RG, Storm T, Baker EF, et al. A controlled study of lysergide in the treatment of alcoholism, 1: the effects on drinking behavior. *Q J Stud Alcohol*. 1966;27(3):469–482.
122. Bernasconi F, Schmidt A, Pokorny T, et al. Spatiotemporal brain dynamics of emotional face processing modulations induced by the serotonin 1A/2A receptor agonist psilocybin. *Cerebral Cortex*. 2014;24(12):3221–3231.
123. Zegans LS, Pollard JC, Brown D. The effects of LSD-25 on creativity and tolerance to regression. *Arch Gen Psychiatry*. 1967;16(6):740–749.
124. Wikler A, Haertzen CA, Chessick RD, et al. Reaction time ("mental set") in control and chronic schizophrenic subjects and in postaddicts under placebo, LSD-25, morphine, pentobarbital and amphetamine. *Psychopharmacology (Berl)*. 1965;7(6):423–443.
125. Pokorny T, Preller KH, Kometer M, et al. Effect of psilocybin on empathy and moral decision-making. *Int J Neuropsychopharmacol*. 2017;20(9):747–757.
126. Middlefell R. The effects of LSD on body sway suggestibility in a group of hospital patients. *Br J Psychiatry*. 1967;113(496):277–280.
127. Griffiths RR, Richards WA, McCann U, et al. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl)*. 2006;187(3):268–283, discussion 284–292.
128. Schmidt A, Kometer M, Bachmann R, et al. The NMDA antagonist ketamine and the 5-HT agonist psilocybin produce dissociable effects on structural encoding of emotional face expressions. *Psychopharmacology (Berl)*. 2013;225(1):227–239.
129. Pasquini L, Palhano-Fontes F, Araujo DB. Subacute effects of the psychedelic ayahuasca on the salience and default mode networks. *J Psychopharmacol*. 2020;34(6):623–635.
130. Denson R, Sydiaha D. A controlled study of LSD treatment in alcoholism and neurosis. *Br J Psychiatry*. 1970;116(533):443–445.
131. Hollister LE, Shelton J, Krieger G. A controlled

comparison of lysergic acid diethylamide (LSD) and dextroamphetmine in alcoholics. *Am J Psychiatry*. 1969;125(10):1352–1357.
132. Lewis CR, Preller KH, Kraehenmann R, et al. Two dose investigation of the 5-HT-agonist psilocybin on relative and global cerebral blood flow. *Neuroimage*. 2017;159:70–78.
133. Mason NL, Kuypers KPC, Müller F, et al. Me, myself, bye: regional alterations in glutamate and the experience of ego dissolution with psilocybin. *Neuropsychopharmacology*. 2020;45(12):2003–2011.
134. Savage C, McCabe OL. Residential psychedelic (LSD) therapy for the narcotic addict: a controlled study. *Arch Gen Psychiatry*. 1973;28(6):808–814.
135. Griffiths RR, Johnson MW, Richards WA, et al. Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. *J Psychopharmacol*. 2018;32(1):49–69.
136. Ditman KS, Moss T, Forgy EW, et al. Dimensions of LSD, methylphenidate and chlordiazepoxide experiences. *Psychopharmacology (Berl)*. 1969;14(1):1–11.
137. Haertzen CA. Changes in correlation between responses to items of the Addiction Research Center Inventory produced by LSD-25. *J Psychopharmacol*. 1966;1(1):27–36.
138. Robinson JT, Davies LS, Sack EL, et al. A controlled trial of abreaction with lysergic acid diethylamide (LSD-25). *Br J Psychiatry*. 1963;109(458):46–53.
139. Spitzer M, Thimm M, Hermle L, et al. Increased activation of indirect semantic associations under psilocybin. *Biol Psychiatry*. 1996;39(12):1055–1057.
140. Holze F, Vizeli P, Ley L, et al. Acute dose-dependent effects of lysergic acid diethylamide in a double-blind placebo-controlled study in healthy subjects. *Neuropsychopharmacology*. 2021;46(3):537–544.
141. Holze F, Gasser P, Müller F, et al. 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. *Biol Psychiatry*. 2023;93(3):215–223.
142. 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.
143. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. *J Psychopharmacol*. 2008;22(6):603–620.
144. Reissig CJ, Carter LP, Johnson MW, et al. High doses of dextromethorphan, an NMDA antagonist, produce effects similar to classic hallucinogens. *Psychopharmacology (Berl)*. 2012;223(1):1–15.
145. Goodwin GM, Aaronson ST, Alvarez O, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. *N Engl J Med*. 2022;387(18):1637–1648.
146. Furukawa TA, Noma H, Caldwell DM, et al. Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. *Acta Psychiatr Scand*. 2014;130(3):181–192.
147. Başoğlu M, Marks I, Livanou M, et al. Double-blindness procedures, rater blindness, and ratings of outcome: observations from a controlled trial. *Arch Gen Psychiatry*. 1997;54(8):744–748.
148. Rickels K, Lipman RS, Fisher S, et al. Is a double-blind clinical trial really double-blind? a report of doctors' medication guesses. *Psychopharmacology (Berl)*. 1970;16(4):329–336.
149. Brownell KD, Stunkard AJ. The double-blind in danger: untoward consequences of informed consent. *Am J Psychiatry*. 1982;139(11):1487–1489.
150. Warner J, Metcalfe C, King M. Evaluating the use of benzodiazepines following recent bereavement. *Br J Psychiatry*. 2001;178(1):36–41.
151. Himle JA, Abelson JL, Haghightgou H, et al. Effect of alcohol on social phobic anxiety. *Am J Psychiatry*. 1999;156(8):1237–1243.
152. Shlay JC, Chaloner K, Max MB, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. *JAMA*. 1998;280(18):1590–1595.
153. Fergusson D, Glass KC, Waring D, et al. Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials. *BMJ*. 2004;328(7437):432.
154. Grunebaum MF, Galfalvy HC, Choo TH, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. *Am J Psychiatry*. 2018;175(4):327–335.
155. Johns RG, Barkham M, Kellett S, et al. A systematic review of therapist effects: a critical narrative update and refinement to review. *Clin Psychol Rev*. 2019;67:78–93.
156. Hayes JA, McAleavey AA, Castonguay LG, et al. Psychotherapists' outcomes with White and racial/ethnic minority clients: first, the good news. *J Couns Psychol*. 2016;63(3):261–268.
157. Jones BDM, Razza LB, Weissman CR, et al. Magnitude of the placebo response across treatment modalities used for treatment-resistant depression in adults: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(9):e2125531.
158. Devilly GJ, Borkovec TD. Psychometric properties of the Credibility/Expectancy Questionnaire. *J Behav Ther Exp Psychiatry*. 2000;31(2):73–86.
159. Mathew SJ, Wilkinson ST, Altinay M, et al. ELEctroconvulsive therapy (ECT) vs ketamine in patients with treatment-resistant depression: the ELEKT-D study protocol. *Contemp Clin Trials*. 2019;77:19–26.
160. Aday JS, Heifets BD, Pratscher SD, et al. Great Expectations: recommendations for improving the methodological rigor of psychedelic clinical trials. *Psychopharmacology (Berl)*. 2022;239(6):1989–2010.

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Supplementary Material

Article Title: Control Conditions in Randomized Trials of Psychedelics: An ACTTION Systematic Review

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List of Supplementary Material for the article

1. **Appendix 1** Full search strategy

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix 1

Nayak SM, Bradley MK, Kleykamp BA, Strain EC, Dworkin RH, Johnson MW. Control Conditions in Randomized Trials of Psychedelics: An ACTTION Systematic Review. *The Journal of Clinical Psychiatry.*

Full Search Strategy

PubMed:

("Lysergic Acid Diethylamide"[Mesh] OR LSD[tw] OR "Psilocybin"[Mesh] OR psilocybin[tw] OR "Banisteriopsis"[Mesh] OR ayahuasca[tw] OR "Hallucinogens"[Mesh] OR psychedelic[tw] OR "Mescaline"[Mesh] OR mescaline[tw] OR peyote[tw] OR Dimethyltryptamine[tw] OR Dipropyltryptamine[tw])

AND

("Placebos"[Majr] OR placebo[tw] OR "Psychotherapy"[Majr] OR controlled[tw] OR randomized[tw] OR "Randomized Controlled Trial" [Publication Type])

NOT

(review[pt] OR letter[pt] OR meta-analysis[pt] OR "Case Reports"[pt] OR "Editorial"[pt] OR review[pt] OR comment[pt] OR “historical article”[pt])

PsycINFO:

TI ((DE "Hallucinogenic Drugs" OR psychedelic) OR (DE "Lysergic Acid Diethylamide" OR LSD OR lysergic) OR (DE "Psilocybin" OR psilocybin) OR (DE "Mescaline" OR mescaline) OR (DE "Peyote" OR peyote) OR dimethyltryptamine OR dipropyltryptamine OR (Ayahuasca OR banisteriopsis))

OR

AB ((DE "Hallucinogenic Drugs" OR psychedelic) OR (DE "Lysergic Acid Diethylamide" OR LSD OR lysergic) OR (DE "Psilocybin" OR psilocybin) OR (DE "Mescaline" OR mescaline) OR (DE "Peyote" OR peyote) OR dimethyltryptamine OR dipropyltryptamine OR (Ayahuasca OR banisteriopsis))

AND

((DE "Treatment") OR (DE "Psychotherapy" OR psychotherapy) OR (DE "Placebo" OR placebo) OR (DE "Randomized Clinical Trials" OR DE "Randomized Controlled Trials") OR controlled OR randomized)

In addition, methodology filters for empirical study, quantitative study, longitudinal study, clinical trial, and followup study were used.

Embase:

lsd:ti,ab,kw OR 'lysergic acid diethylamide':ti,ab,kw OR 'psilocybine'/de OR psilocybin:ti,ab,kw OR 'banisteriopsis'/de OR ayahuasca:ti,ab,kw OR psychedelic:ti,ab,kw OR hallucinogen:ti,ab,kw OR

‘mescaline’/de OR mescaline:ti,ab,kw OR peyote:ti,ab,kw OR 'n,n dimethyltryptamine'/de OR dimethyltryptamine:ti,ab,kw OR dipropyltryptamine:ti,ab,kw

AND

'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'placebo'/de OR placebo:ti,ab,kw OR psychotherapy/de OR controlled:ti,ab,kw OR randomized:ti,ab,kw

NOT

‘Least significant difference’:ti,ab,kw OR ‘LSD post hoc’:ti,ab,kw OR ‘LSD post-hoc’:ti,ab,kw OR ‘LSD test’:ti,ab,kw OR ‘LSD test’:ti,ab,kw OR ‘Fisher/s LSD’:ti,ab,kw OR ‘lysosomal storage disease’:ti,ab,kw OR 'low sodium diet':ti,ab,kw

AND

[embase]/lim NOT ([embase]/lim AND [medline]/lim)

NOT

'conference abstract'/it

AND

'human'/de