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REVIEW

ADDICTION SSA

Psychedelic-assisted treatment for substance use disorder: A narrative systematic review

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Abstract

Background and aims: This is the first systematic review of the extant literature on all major psychedelic-assisted treatment for alcohol use disorder (AUD), tobacco use disorder (TUD) and other substance use disorders (SUD). We aimed to summarise the evidence for efficacy of psychedelic-assisted treatment for AUD, TUD, and SUD; to evaluate its quality; and to offer recommendations for research.

Methods: This was a prospectively registered narrative systematic review of open-label, randomised controlled trials (RCT), and observational studies of d-lysergic acid diethylamide (LSD), mescaline, psilocybin, ayahuasca, ketamine, ibogaine and 3,4-methylenedioxymethamphetamine (MDMA). Eligible studies had SUD outcome measures including craving, substance use, relapse, and remission. Study quality was evaluated using the Cochrane Collaboration Risk of Bias (RoB), and Cochrane Collaboration RoB in Non-randomised Studies of Interventions tool. Certainty of evidence for RCTs was judged using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tool.

Findings: 37 studies (2035 participants) were reviewed: LSD (14; n = 1047); mescaline (1; n = 7); psilocybin (4; n = 135); ayahuasca (3; n = 101); ketamine (10; n = 579); ibogaine (5; n = 166); and MDMA (1; n = 14). There were no serious adverse events reported in any study. A two-centre, placebo-controlled, phase 2 superiority RCT of psilocybin for AUD, and a two-centre, double-blind, four-arm, placebo-controlled phase 2 RCT of ketamine for AUD yielded the best evidence of efficacy. Progression support to a phase 3 trials was secured from an open-label phase 2 study of psilocybin for TUD and nine phase 2 RCTs of ketamine for AUD, cannabis use disorder, cocaine use disorder, and opioid use disorder (all nine with high-RoB and low-GRADE evidence certainty).

Conclusions: Psilocybin-assisted treatment for alcohol use disorder appears to have the best evidence of efficacy among all major psychedelic-assisted treatments for alcohol, tobacco, and other substance use disorders. Future research of psychedelic-assisted treatment should report all safety events; screen for person-level characteristics indicating that psychedelic-assisted substance use disorders treatment is contraindicated; strive to mitigate blinding of participants to interventions; use factorial designs for drug and

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psychotherapy randomised controlled trials; and build consensus for a field-specific Core Outcome Set.

KEYWORDS
alcohol use disorder, cannabis use disorder, cocaine use disorder, psychedelic-assisted treatment, substance use disorder, tobacco use disorder

INTRODUCTION

Substance use disorders (SUD)—including amphetamine use disorder (AmUD), cannabis use disorder (CaUD), cocaine use disorder (CoUD), opioid use disorder (OUD) and tobacco use disorder (TUD)—are a longstanding public health concern affecting over 130 million people around the world [1]. In most healthcare systems, maintenance pharmacotherapies are offered to help people with some SUD attenuate their substance craving; block reinforcing effects of the primary substance; and prevent the onset of withdrawal symptoms.

SUD pharmacotherapies include: naltrexone [a full μ-opioid receptor (μ-OR) antagonist] and acamprosate [an *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist] for alcohol use disorder (AUD) [2, 3]; varenicline (a partial selective nicotinic acetylcholine receptor partial agonist), bupropion (a dopamine-reuptake inhibitor) and variously formulated agonist replacement products for TUD [4, 5]; and methadone (a full μ-OR agonist), buprenorphine (a partial μ-OR agonist) and naltrexone [6, 7] for OUD. There are no pharmaceutical products with a market authorisation to treat AmUD, CaUD and CoUD.

The available SUD pharmacotherapies are evidence-supported from RCTs. Various psychosocial interventions are also evidence-supported. Motivational, cognitive-behavioural, contingency management (behavioural reinforcement) and facilitated access to Mutual Aid modalities have been developed to accompany AUD, TUD and OUD medicines and as monotherapies for AmUD, CaUD and CoUD [8, 9]. However, 40% to 60% of patients with SUD do not achieve or maintain a desired response [10]. There are several reasons for this, including: difficulties with adhering to the requirements of the therapy protocol; inadequate SUD symptom control; and leaving treatment against advice, which moderate outcome [10].

In the context of interest in exploring other avenues to treat SUD, there has been longstanding interest in psychedelic drugs [11]. This is a broad and disparate group of drugs that are capable of causing acute and robust change in perception, cognition and affect. It has been argued that psychedelic drugs are attractive treatment candidates because there appears to be rapid development of tolerance with low risk of physiological dependence [12, 13].

For convenience, psychedelics can be classified into two groups—classic and non-classic. With a longer history, the main classic psychedelics are partial or full agonists of the serotonin receptor and include: d-lysergic acid diethylamide (LSD) [14]; mescaline, from the Peyote cactus [15]; psilocybin, from the *Psilocybe* mushroom [16]; and ayahuasca, a brewed drink combining leaves from the *Psychotri viridi* bush containing *N*,*N*-dimethyltryptamine and bark from the *Banisteriopsis caapi* vine containing the harmine [17]. Clinical studies of LSD and mescaline for AUD were first conducted in the late 1950s to the early 1960s [18–21] and later 1960s [22–25].

The main non-classic psychedelics include: the dissociative anaesthetic ketamine, a NMDA receptor antagonist capable of hallucinogenic effects [14]; ibogaine, an NMDA antagonist, κ-OR agonist and serotonin reuptake blocker, from the root bark of the *Tabernanthe iboga* shrub, with dreamlike and introspective effects [26]; and 3,4-methylenedioxymethamphetamine (MDMA), a partial serotonergic agonist with action at serotonin, noradrenaline and dopamine reuptake inhibitors, with empathogenic effects [27]. Clinical studies of ketamine for OUD were conducted in the 1970s, although findings were not reported for several years [28]. MDMA research began in the mid-1980s, mostly consisting of retrospective, qualitative analyses of MDMA-assisted psychotherapy [29]. These early studies of ketamine and MDMA targeted other mental health disorders but included exploratory alcohol and drug use outcomes [29]. In the 1980s, pilot studies of ibogaine were conducted for SUDs in the United States (US) by the National Institute of Drug Abuse [14]. Treatment-emergent serious adverse cardiovascular symptoms appear to have curtailed further study [26], but there has been continued interest in ibogaine for OUD withdrawal management [30].

The psychedelics have had a remarkable cultural history. In the 1960s, recreational use of classic psychedelics was promoted by various counter-culture movements in the United States [14, 31, 32]. The federal authorities view these drugs as posing a serious risk to public health, and in the 1970s, international drug reform [including the US Controlled Substances Act (CSA), the United Kingdom (UK) Misuse of Drugs Act and the United Nations Convention on Psychotropic Substances] established legal scheduling of LSD, mescaline, psilocybin and MDMA and brought about a prohibition in clinical research [33]. To some extent, ketamine stood apart. Although scheduled in 1999 by the CSA, there was continued investigation of ketamine-assisted treatment for SUD [14]. From the 2000s, there was a resurgence of interest in psychedelic-assisted treatment for SUD. Ketamine, psilocybin, ayahuasca and ibogaine have been the focus of clinical studies for AUD [34–37], TUD [38, 39], OUD [40–42], CoUD [43, 44] and polydrug-SUD (PSUD) [45, 46].

Concerns have been raised of overly strong claims for efficacy [47]. In 2012, Krebs and Johansen [48] conducted a meta-analysis of LSD-assisted treatment for AUD. Among three trials that reported maintained abstinence from alcohol use, there was a statistically significant effect associated with LSD after 1- and 3-month follow-up (OR = 2.07; 95% CI = 1.26–3.42; *P*-value 0.004); and also, after 2- and 3-month post-treatment (OR = 1.80; 95% CI = 1.07–3.04;

P-value 0.03). The effect was not seen at a 6-month follow-up (OR = 1.42; 95% CI = 0.65–3.10; *P*-value 0.38).

In 2020, Fuentes and colleagues [49] reviewed the efficacy of LSD for a range of psychiatric disorders including AUD and OUD. They drew positive conclusions, but contended that considerable study heterogeneity (because of the wide range of psychedelic doses, psychotherapies, comparators, outcome measures and follow-ups) precluded a valid meta-analysis. Reviews of ketamine and ibogaine for AUD, CoUD and OUD have also been conducted [50–54].

There has been no systematic review of the extant literature on all classic and non-classic psychedelic-assisted treatments for SUD. We judged that such a stock-take would be of value to the addiction science community. Our aim was to summarise the evidence for efficacy, to evaluate its quality and to offer recommendations for research.

METHODS

Design and search strategy

This was a systematic review of efficacy studies of classic (LSD, mescaline, psilocybin and ayahuasca) and non-classic (ketamine, ibogaine and MDMA) psychedelic-assisted treatment for SUD. The protocol was prospectively registered on the International Prospective Register of Systematic Reviews (ID: CRD42022320608). The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [55].

Study selection

Eligible articles reported on RCTs, open-label uncontrolled trials and observational cohort studies that had SUD-specific outcome measures including craving for substances, substance use, relapse and remission. We included studies of treatment for mental health disorders if there was a SUD efficacy outcome as a primary measure. We screened for serious adverse events (SAE). We excluded single patient case studies and studies of psychedelic-assisted withdrawal management.

We searched the Cochrane CENTRAL (PubMed, Embase, CINAHL), OVID (PsycINFO, Embase, Embase Classic) and Web of Science (Core Collection) databases for articles (no date restriction) published in the English language that report findings from an experimental or observational study of individuals diagnosed with a SUD [Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) systems] who were offered psychedelic-assisted treatment.

Studies were identified using the following key search terms: *LSD*, *psilocybin*, * ibogaine*, *ayahuasca or dimethyltryptamine*, *ketamine*, *MDMA*, *salvia*, *alcohol use disorder*, *opioid use disorder*, *stimulant use disorder*, *amphetamine use disorder*, *cocaine use disorder*, *tobacco use disorder*, *psychotherap* or *psycholytic* or *psychedelic-assisted* or *psychedelic peak*. Key words were exploded or adjusted per database to capture the varying names used across the literature.

We cross-referenced our search in Google Scholar and looked for articles on the websites of Awakn Life Sciences, Beckley PsyTech and the Multidisciplinary Association for Psychedelic Studies (MAPS). Searches were done in two iterations. The first was completed in September 2023, the second in June 2024. We expected to use the Newcastle-Ottawa Scale (NOS) to assess observational studies [56], but in the end no study had a design that included a non-psychedelic exposed comparison group.

Study selection and summary

Independently, three reviewers (T.P., F.S. and S.B.) screened each citation by abstract, title level and full text. Disagreements regarding the inclusion of a study were resolved through consensus discussion with J.M. Using the PICOS template (i.e. population, intervention, comparison, outcome and setting), the three reviewers then tabulated the following information for each study: author/date, country, design/setting, participant characteristics, experimental and control interventions, outcome measures and findings. For the latter, we tabulated rates, differences, efficacy parameters, effect sizes and the *P*-value of test statistics. For economy, the term 'significant' means 'statistically significant' (i.e. *P*-value <0.05).

Quality and risk of bias

For RCTs, we used the Cochrane Collaboration risk of bias (RoB) tool to assess the following factors that could introduce bias: the randomisation process; knowledge of condition assignment; adherence to the intervention; management of missing outcome data; measurement of outcome; and reporting of findings [57]. Taking these together, the RoB of each study was classified as low, some concerns or high. RoB for non-randomised clinical trials was assessed using the Cochrane Collaboration RoB in non-randomised studies of interventions (ROBINS-I) tool, classifying each study as low, moderate, serious or critical [58]. We also rated the overall certainty of efficacy evidence for RCTs using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool [59]. GRADE assigns the certainty of evidence as very low, low, moderate or high. Low–high ratings may be down rated because of: RoB; imprecision in estimated efficacy; effect inconsistency; indirectness in outcome assessment; and potential publication bias. GRADE guidelines for narrative synthesis were followed [60].

RESULTS

Identified articles

Our search of electronic databases identified 776 citations (386 from CENTRAL, 229 from Ovid and 161 from Web of Science). A further 30 citations were found elsewhere: two from Awakn Life Science; three from MAPS; seven from Google Scholar; and 18 from the reference lists of previous reviews.

After the removal of 126 duplicates, 757 studies were screened at the title and abstract level. Of these, 684 were ineligible and excluded. Full text examination was then done on 73 studies, with a further 36 articles judged ineligible (reasons in Figure 1). The included 37 studies included 2035 participants as follows: LSD (14 studies; 1047 participants); mescaline (one study; seven participants); psilocybin (four studies; 135 participants); ayahuasca (three studies; 101 participants); ketamine (10 studies; 579 participants); ibogaine (five studies; 166 participants); and MDMA (one study; 14 participants). Overall, 14 of 37 articles (37.8%) reported on adverse events. No SAE were reported. Tables 1 and 2 summarise the key information from each study by psychedelic and SUD, respectively.

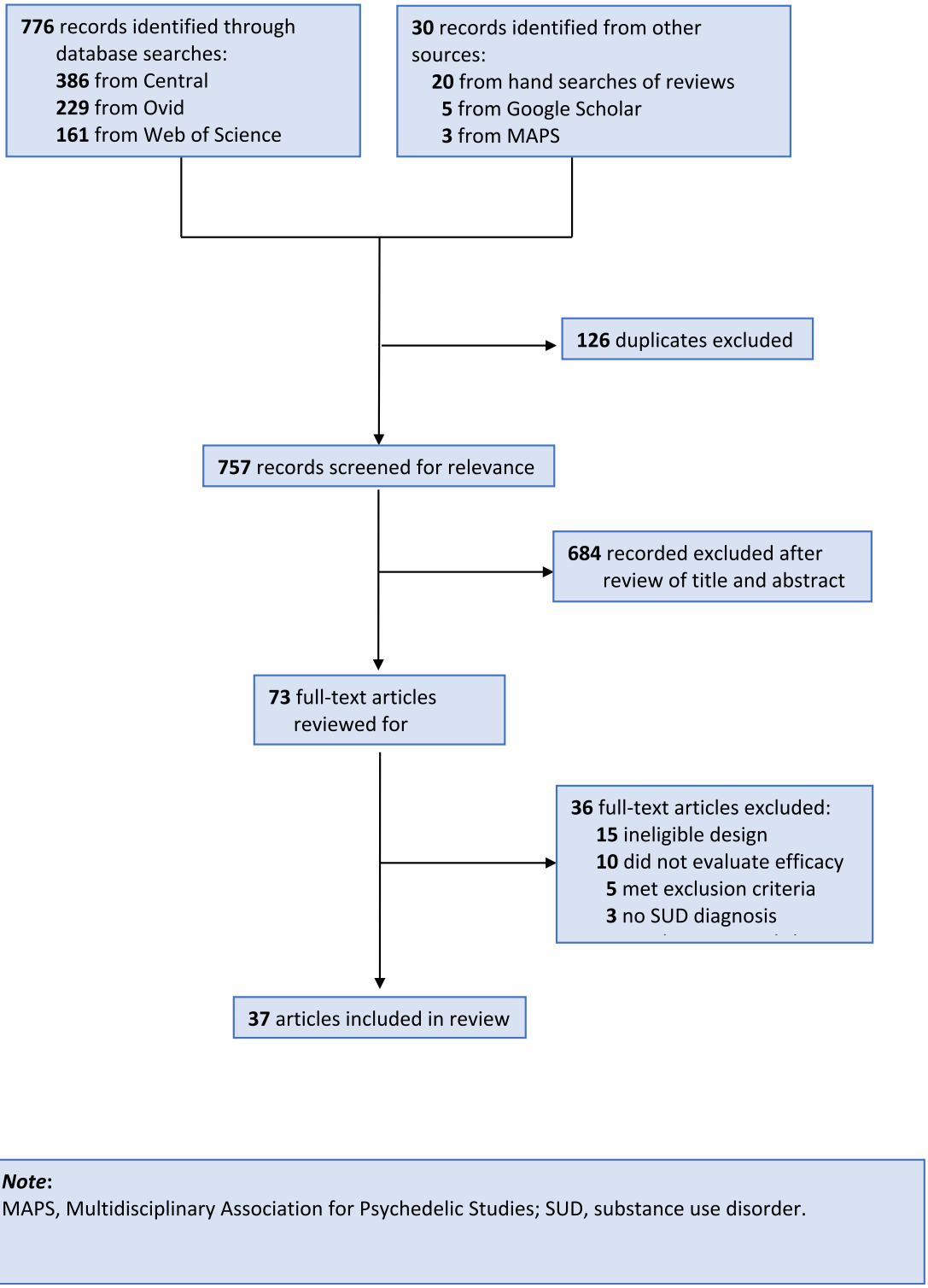

FIGURE 1 Study selection process.

TABLE 1 Evidence summary—classic psychedelics.

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
LSD–AUD					
Smith *et al*., 1958 [18], Canada	Uncontrolled pilot (inpatient)	*n* = 17; *M* = 12 y 'uncontrolled drinking'	One dose (*n* = 12) Several doses (*n* = 5)	Abstinence (2 mo–2 y); reduced drinking; relapse	Abstinence: 3/17; reduced drinking: 4/17; no change: 10/17; relapse: 1/17
Chwelos *et al*., 1959 [19], Canada	Uncontrolled pilot (inpatient)	AUD (*n* = 16); *M* = 11.6 y heavy drinking	LSD (200–400 mcg)	Abstinence (2–9 mo)	Abstinence: 10 pts; reduced drinking: 5 pts. no change:1 pts
MacLean *et al*., 1961 [20], Canada	Open-label pilot (inpatient)	AUD (*n* = 61) male *n* = 50; Female *n* = 11; *M* = 14.36 y 'uncontrolled drinking' Average number of hospital admissions 8.07	LSD (400–1500 mcg)	Abstinence (3–18 mo; median 9.1 mo)	Abstinence: 30 pts; reduced drinking:16 pts; no change: 15 pts
O'Reilly and Reich, 1962 [21], Canada	Open-label pilot (inpatient)	AUD (*n* = 18)	LSD (200 mcg) (+100 mcg to patients unresponsive to 200 mcg)	Abstinence (7–88 weeks)	Abstinence: 2 pts; reduced drinking: 6 pts; no change: 3 pts; lost to follow up: 6 pts; not accounted for: 1
Jensen and Ramsay, 1963 [63], Canada	Non-randomised controlled trial (inpatient)	AUD (*n* = 125); males 24–65 y; *M* age = 39.3 y	LSD (200 mcg) (group therapy, psychotherapy, AA meetings, individuals' psychotherapy (*n* = 70)) Individual psychotherapy only (*n* = 55)	Abstinence (6–18 mo); relapse	LSD therapy: Abstinence: 39 pts; reduced drinking: 7 pts; no change: 16 pts; lost to follow up: 8 pts Individual therapy: Abstinence: 8 pts; reduced drinking: 4 pts; no change: 17 pts; lost to follow up 26 pts; relapse: 1 pt (within 2 weeks) LSD therapy group had significantly more abstinence/reduction rates than controls at follow-up ($P > 0.1$)
Smart *et al*., 1966 [66], Canada	RCT (inpatient and day care)	AUD (*n* = 30); females (*n* = 2); males (*n* = 28); *M* = age 40 y	I: single dose LSD (800 mcg) (*n* = 10) C: ephedrine sulphate (60 mg) (*n* = 10) C: no drugs (*n* = 10), individual/group psychotherapy	Drinking History Questionnaire; % change in abstinence (6 mo); no. of drinking occasions; drunkenness occasions	Improved abstinence in all 30 pts; LSD = 33.7%; ephedrine = 31.5%; control = 19.6%; no significant differences between other group outcomes ($P > 0.05$)
Dusen *et al*., 1967 [62], USA	Open-label pilot (inpatient)	AUD (*n* = 99); all females; *M* = age 41 y; *M* = 7.82 y excessive drinking	C: originally scopolamine (*n* = 28) (this was later dropped) I: pilot LSD (average 400 mcg; range 100–800 mcg; *n* = 15) I: experimental LSD (average 400 mcg,	Abstinence (6, 12 and 18 mo)	No significant differences between pre-LSD, pilot LSD, experimental LSD or between multiple LSD sessions At 18 mo average drinking scores: pre-LSD: 4.03; pilot LSD:

(Continues)

TABLE 1 (Continued)

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
			range 100–800 mcg; total *n* = 56); LSD sessions; 1 (*n* = 29); 2 (*n* = 19); 3 (*n* = 9) (based on severity of alcoholism using MindLin Index)		3.70; experimental LSD: 3.97
Hollister *et al*., 1969 [22], USA	RCT (inpatient)	AUD (*n* = 72); all males; age 21–50 y; acute AUD episode within 2 weeks of selection or an alcohol hospital admission	I: single dose LSD (600 mcg) (*n* = 37) C: D-amphetamine (60 mg) (*n* = 35)	DBS (total degree of impairment because of drinking at 2 and 6 mo)	I: Abstinent 8/37; reduced drinking 5/37; unchanged12/37; worse 1/37; lost to follow up 11/37 C: Abstinent 7/35; reduced drinking 2/35; unchanged 9/35; worse 1/35; lost to follow up 16/35 Significant improvements in LSD pts vs. controls at 2-mo follow up ($P < 0.01$); no significant difference reported at 6 mo
Ludwig *et al*., 1969 [23], USA	RCT (inpatient)	AUD (*n* = 176); all males; age 21–55 y; with up to four past alcohol-related hospital admissions	LSD (*n* = 132) I: hypnodelic therapy LSD (3 mcg/kg, *M*: ∼210 mcg) + 3-h hypnosis + psychotherapy I: psychedelic therapy, LSD (3 mcg/kg, *M*: ∼210 mcg) + psychotherapy I: drug therapy, LSD (3 mcg/kg, *M*: ∼210 mcg) + silent observation C: milieu therapy, no drug (*n* = 44)	Abstinence and relapse (1–12 mo); Behaviour Rating Scale (6, 12 mo)	Abstinence: At 1 mo LSD 94/132, control 25/44; at 3 mo LSD 41/132, control 11/44; at 6 mo LSD 24/132, control 9/44 Relapse across all groups at 3 mo (65%) and 12 mo (80%–90%); Behaviour Rating Scale: significant improvements in all groups ($P < 0.05$); no significant differences between groups
Johnson, 1969 [64], Canada	RCT (inpatient/ outpatient)	AUD (*n* = 95); female (*n* = 8); male (*n* = 87); *M* age = 40.9 y	I: 300 mcg LSD + 264 mcg (*M*) 1 h later. Nurse present, but no therapist (*n* = 23) I: 300 ug LSD + 264 mcg (*M*) 1 h later. Nurse + therapist present (*n* = 25) C: 3.75 g sodium phenobarbital + 30 mg methamphetamine hydrochloride (*n* = 22) C: routine care with no hospitalisation (*n* = 25)	Abstinence; drinking practices/ consequences of drinking (12 mo); attitudes toward drinking	Abstinence/drinking practices: Significant improvements in all groups $P < 0.01$ No significant differences between treatment groups
Bowen *et al*., 1970 [61], USA	RCT (inpatient)	AUD (*n* = 59); all males veterans; median 44.5 AUD	I: single dose LSD (500 mcg) (*n* = 22) C: single dose active placebo LSD (25 mcg) (*n* = 22)	Adjustment scale (12 mo)	All groups showed improvements, but no significant differences at 1-y follow-up between groups

TABLE 1 (Continued)

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
			C: no drug (*n* = 15)		
Pahnke *et al*., 1970 [65], USA	RCT (inpatient)	AUD (*n* = 117); all male; age unknown	I: single high dose LSD (350–450 mcg) (*n* = 73) C: single low dose LSD (50 mcg) (*n* = 44), individual psychotherapy	DBS (6 mo); GA (6 mo)	13/117 were lost to follow up. Improved GA score at 6 mo; high dose 28/64 (44%); low dose 10/40 (25%) improved DBS at 6 mo; high dose 34/64 (53%); low dose 13/40 (33%) Significant differences between GA ($P < 0.05$) and DBS ($P < 0.025$)
Tomsovic and Edwards, 1970 [24], USA	RCT (inpatient)	AUD (*n* = 97); all males; 12 y problematic drinking; *M* age = 43 y	I: single dose LSD (500 mcg) (*n* = 52) C: TAU (*n* = 45), group psychotherapy	Drinking Adjustment Scale (3, 6 and 12 mo)	At 12 mo; LSD: Abstinence 14/52; much improved 4/52; slightly improved 9/52; unchanged 5/52; lot to follow up 20/52. TAU: Abstinence 3/45; much improved 5/45; slightly improved 9/45; unchanged 9/45; lot to follow up 219/52 Significant improvement in abstinence in patients receiving LSD at 1 y vs. control ($P < 0.01$)
LSD–OUD					
Savage and McCabe, 1973 [25], USA	RCT (aftercare clinic for paroled addicts—correctional institution)	Heroin addiction (*n* = 74); all males	I: single dose LSD (200–500 mcg) (*n* = 37); 4–6-week therapy programme in a halfway house facility C: Treatment as usual (*n* = 37)	GARS; abstinence (6, 12 mo); relapse	Significant improvement in abstinence in patients receiving LSD ($P < 0.05$) Across 12 mo: Total abstinence; 9/37 LSD; 2/37 control. 3/37 in the LSD group relapsed but then went on to achieve 12 mo abstinence No significant differences between groups in global adjustment
Mescaline–OUD					
Smith *et al*., 1958 [18], Canada	Open-label pilot (inpatient)	OUD (*n* = 7); *M*: 12 y 'uncontrolled drinking'	Single dose mescaline (0.5 g); psychotherapy	Abstinence (including small amounts) 2 mo–2 y; *M* = 1 y); reduced drinking; relapse	Abstinence after mescaline: 3 pts; reduction in drinking 2 pts; no change in 2 pts
Psilocybin–TUD					
Johnson *et al*., 2014 [38], USA		TUD (*n* = 15); female (*n* = 5); male (*n* = 10);	I: 3 psilocybin sessions; week 5 (moderate	Abstinence: Intake, weekly, 6-mo	Abstinence: 12/15 achieved 7 days at

(Continues)

TABLE 1 (Continued)

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
	Open-label pilot (outpatient)	*M age* = 51 y with tobacco addiction	dose 20 mg/70 kg); week 7 and 13 (high dose 30 mg/70 kg); 4 smoking cessations CBT sessions/2 group-based smoking cessation therapy sessions	(biological markers) and after each therapy sessions (TLFB); QSU; SASE (intake, weekly, 6-mo follow-up)	6 mo [TLFB ($P < 0.001$), breath CO ($P < 0.01$) and Urine Cotinine ($P < 0.05$)]; relapse: 4/15 in the 16-week period between end of treatment and 6-mo follow-up Significant differences in QSU and confidence to abstain ($P < 0.001$) across all time points
Johnson *et al*., 2017 [39] USA,	Long-term follow-up (outpatient)	Follow-up of the same pts as Johnson *et al*., *n* = 12 returned for follow up (2014)	Refer to Johnson *et al*. 2014 intervention	Abstinence: 12 and 30 mo (smoking biomarkers); intake, 10 weeks, 6 mo, 10 weeks, 12 mo, and 30 mo (TLFB)	10/12 at 12-mo biological abstinent; 8/12 self-confirming continued abstinence since treatment. 9/12 at 30-mo biologically abstinent; 7/12 self-confirming continued abstinence Significant reduction in abstinence intake to 30 mo post treatment ($P < 0.001$)
Psilocybin–AUD					
Bogenschutz *et al*., 2015 [34], USA	Proof-of-concept study (outpatient)	AUD (*n* = 10); female (*n* = 4); male (*n* = 6); 2 heavy drinking days in the last 30 days; concerned but not currently in treatment	I: 2× psilocybin doses. One after session 4 and 8 of psychosocial intervention 12-week psychosocial intervention programme (preparation sessions; MET; debrief sessions)	Drinking behaviour (TLFB) (12 weeks preceding enrolment, mo 1–9) Penn Alcohol Craving Scale (baseline, weeks 4, 5, 8, 9, 12, 24, 36) Alcohol Abstinence Self-Efficacy Scale (baseline, weeks 4, 5, 8, 9, 12, 24, 36)	Significantly lower PDD during weeks 5–12 vs. baseline ($P = 0.009$). Effect stable during weeks 25–36 ($P = 0.007$) Significantly lower PHDD in weeks 5–12 vs. baseline ($P = 0.008$). Effect stable during weeks 25–36 ($P = 0.004$) Significant improvements in cravings in week 8, 9, 12 and 36 vs. baseline Significant improvement in temptation to use at week 9 and 24 vs. baseline ($P < 0.05$) Significant improvement in confidence to abstain at week 5 vs. baseline ($P < 0.05$)
Bogenschutz *et al*., 2022 [37], USA	Double blind RCT (outpatient)	AUD (*n* = 95); females (*n* = 42); males (*n* = 53); *M* age = 46 y (SD = 12 y); 4 heavy drinking days in the last 30	2× psilocybin dosing sessions Week 4: I: Psilocybin (25 mg/70 kg) (*n* = 48) C: Diphenhydramine (50 mg) (*n* = 45)	PHDD; PDD; DPD; abstinence by no. of HD) and WHO risk levels [1–3]	Lower PHDD, PDD, DPD and HDD in pts receiving psilocybin vs. control at 32-week follow-up: psilocybin (PHDD: $P = 0.01$, PDD:

TABLE 1 (Continued)

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
			Week 8: I: Psilocybin (25–40 mg/70 kg) (*n* = 43) C: diphenhydramine (50–100 mg) (*n* = 35) 0.12 Psychotherapy sessions: MET and CBT (pre-medication, between 1st and 2nd medication and during month 4 post-medication)[a]		*P* = 0.05, DPD: *P* = 0.01, HDD: *P* = 0.01) No significant abstinence across groups during weeks 5–36, but it was significantly different during weeks 33–36 The psilocybin group had a significant 2-level reduction in WHO risk during weeks 5–36 vs. controls (*P* = 0.049)
Ayahuasca–PSUD					
Thomas *et al*., 2013 [45], Canada	Observational (First Nations Community)	PSUD (*n* = 12)	Two ayahuasca ceremonies and group counselling	ASSIST 4WSUS (intake and 6 mo)	At follow up: Alcohol consumption reduced by 30%; tobacco reduced by 18.2%; cocaine reduced by 60%; significant reductions in problematic cocaine use (*P* < 0.05)
Berlowitz *et al*., 2019 [67], Peru	Observational (inpatient)	PSUD (*n* = 53); all males; cannabis (*n* = 26); alcohol (*n* = 23); cocaine (*n* = 22); opiates (*n* = 5); amphetamines/ stimulants (*n* = 4); tranquilisers (*n* = 4); *M* age = 30.86 y	Traditional Amazonian plant medicine, including ayahuasca and psychotherapy, relapse prevention, psychodrama	ASI-5 (T1, T2) CEQ (T1, T2)	36/53 completed; 17/53 dropped out Significant reductions in addiction severity for alcohol and drug use (*P* < 0.001) and craving (*P* < 0.001)
O'Shaughnessy *et al*., 2021 [68], Peru	Observational (inpatient)	PSUD (*n* = 36); all males; *M*: age 29; alcohol; cannabis; cocaine	Ayahuasca (dose not reported) Amazonian and Western psychotherapeutic program	Craving (CEQ 2–12 mo follow-up); addiction severity (intake only)	22/36 completed; 14/36 dropped out Significant changes in craving (*P* < 0.001); improvements were observed early into treatment and were maintained throughout

Note: Studies that used the same sample have been identified. Where appropriate significant values have been provided.
Abbreviations: 4WSUS, 4 Week Substance Use Scale; ASI-5, Addiction severity index; ASSIST, Alcohol, Smoking and Substance Involvement Screening Test; AUD, alcohol use disorder; C, control; CBT, cognitive behavioural therapy; CEQ, Craving Experience Questionnaire; DBS, Drinking Behaviour scores; DPD, drinks per day; GA, Global Adjustment; GARS, Global Adjustment Rating Scale; HDD, heavy drinking days; I, Intervention; LSD, d-lysergic acid diethylamide; *M*, mean; MET, motivational enhancement therapy; mo, months; OUD, opioid use disorder; PDD, percentage of drinking days; PHDD, percentage of heavy drinking days; pts, participants; QSU, Questionnaire on smoking urges; TAU, treatment as usual; TUD, tobacco use disorder; SASE, Smoking Abstinence Self-Efficacy Scale; TLFB, timeline follow back; WHO, World Health Organisation.
[a]Two participants initially recruited were absent from results.

Because the Krebs and Johansen meta-analysis [48] had combined the effects of LSD on abstinence for AUD we did not repeat this. For the other psychedelics, there was considerable study heterogeneity relating to outcome instruments and measures and the timing of follow-ups, which precluded meta-analysis. Therefore, a narrative synthesis was conducted.

TABLE 2 Characteristics and results of included studies—non-classic psychedelics.

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
Ketamine–AUD					
Krupitsky and Grinenko 1997 [28], Russia	RCT (inpatient)	Alcoholics (*n* = 211); male only *M* age, 36.5 y	I: ketamine 2.5 mg/kg (*n* = 111) C: TAU (*n* = 100) Both underwent a 3-month treatment course	Abstinence and relapse (%) at 1 y; ketamine only and at 2 and 3 y	Abstinence at 1 y; KPT group 73/111; TAU 24/100; significantly higher in KPT vs. control ($P < 0.01$) Relapsed at 1 y; KPT 30/111; TAU 69/100 At 3 y 42/111 KPT group was examined; 14/42 abstinent; 24/42 relapsed; 4 could not be obtained; TAU was not followed up to 3 y
Dakwar *et al*., 2020 [69] USA	RCT (outpatient)	AUD (DSM-IV), (*n* = 40); female (*n* = 21); male (*n* = 19); *M* age, 53 y, minimum daily or weekly use; seeking treatment	I: ketamine (0.71 mg/kg; (*n* = 17)) C: midazolam (0.025 mg/kg) (*n* = 23) MET for 5 weeks	Abstinence (%) at 21 days and 6 months; measured by urine ethyl glucuronide screen; time to relapse	Abstinence at 21 days; KPT 9/17; control 9/22; abstinence at 6 months collected from 19/40 pts; KPT 6/8; control 3/11 Time to relapse significantly longer in ketamine group (*P*-value = 0.04)
Grabski *et al*., 2022 [36], UK	RCT (outpatient)	Moderate–severe AUD (DSM-IV): (*n* = 96); female (*n* = 35); male (*n* = 61) *M* age, 44 y	4 treatment arms (8 visits) I: ketamine + psychotherapy (*n* = 24) I: ketamine + psychoeducation (*n* = 24); C: saline + psychotherapy (*n* = 23) C: saline + psychoeducation (*n* = 25) Saline (0.9%) or i.v. infusions of ketamine (0.8 mg/kg) at visits 2, 4 and 6 MBRP at visits 2–8	Verified alcohol relapse at 6 months; self-reported (%) days abstinent at 3 and 6 months (alcohol TLFB)	Relapsed at 3 months; Ketamine + PT 12/21, Ketamine + PE 13/22, saline + PT 13/21; saline + PE 17/21; relapse at 6 months; Ketamine + PT 13/21, Ketamine + PE 15/22, saline + PT 14/21, saline + PE 18/21; significantly higher abstinent at 6 months for ketamine vs.

TABLE 2 (Continued)

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
					placebo (*MD* = 10.1, 95% CI = 1.1, 19.0); no significant differences were found for relapse within 6 months
Ketamine–OUD					
Krupitsky *et al*., 2002 [40], Russia	RCT (inpatient)	OUD (*n* = 70); high dose (*n* = 35; female *n* = 8; male *n* = 27; *M* age, 23 y); low dose (*n* = 35′; female, *n* = 7; male, *n* = 28)	I: KPT (2.0 mg/kg i.m.) C: non-hallucinogenic dose of KPT (0.2 mg/kg i.m.)	Abstinence at baseline and months 1–12, 15, 18, 21 and 24; craving (VAS) at baseline, after KPT and at months 1, 3, 6, 12, 18 and 24	Significantly greater abstinence in high dose vs. low dose at months 1–2 ($P < 0.01$), 3–6 ($P < 0.05$), and 8–24 ($P < 0.05$); decreased *M* craving VAS score in high dose group compared to pre-KPT immediately post-KPT up to 24 months ($P < 0.001$) and for low dose group compared to pre-KPT immediately post-KPT up to 1 month ($P < 0.01$); significant difference between low and high dose groups immediately post-KPT ($P > 0.001$), and at 1 month ($P < 0.05$) and 3 months ($P < 0.01$)
Krupitsky *et al*., 2007 [41], Russia	RCT (active drug control impatient/ outpatient)	Heroin dependence (*n* = 53); female (*n* = 9), male (*n* = 44) *M* age, 22.6 y	C: single KPT (*n* = 27) (2 mg/kg ketamine i.m.) I: multiple KPT (3 session) (*n* = 26) (2 mg/kg ketamine i.m.) Addiction counselling session before each KPT session; single KTP group received addiction	Abstinence rate (%) across 12-month follow-up; craving (VAS-C) measured before and after each KPT or addiction	Abstinence: 13/26 multiple KPT; 6/27 single KPT; significant greater abstinence up to 12 months in

(Continues)

TABLE 2 (Continued)

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
			counselling sessions on same timescale as multiple KPT sessions (at 1 and 2 months after first KPT session)	counselling session, and at months 1, 3, 6, 9 and 12	multiple KPT ($P < 0.05$) Relapsed/ dropped out: 4/26 multiple KPT; 7/27 single KPT Craving decreased for both groups up to follow up, however, no significance was found No significant difference seen between single vs. multiple KPT
Ketamine–CoUD					
Dakwar *et al*., 2014 [43], USA	RCT crossover (3-arm) (inpatient, hospitalised)	Diagnosed CoUD (DSM-IV) ($n = 8$); female ($n = 1$); male ($n = 7$) Not seeking treatment or abstinence *M* age, 21–52 y	I: infusion of lorazepam (2 mg) and 2× ketamine (0.41 mg/kg/0.71 mg/kg i.v.) ($n = 8$) Order randomised for each group (although low dose ketamine always before high dose ketamine); 3 groups total; 48 h between infusions	Craving (VAS) at baseline and post-infusion; motivation to quit URICA Drug use per day ($) and drug using days (of previous 28) at baseline and 4 weeks	Abstinence 2 weeks or more; 4/8; significant reduction in median follow-up drug use vs. baseline ($P < 0.001$), and in *M* use days vs. baseline ($P = 0.012$); significant decreased cue-induced cocaine craving in ketamine vs. lorazepam ($P = 0.012$) Greater change in median URICA score after ketamine vs. lorazepam ($P < 0.05$)
Dakwar *et al*., 2017 [44], USA	RCT crossover (2-arm) (inpatient, hospitalised)	Diagnosed CoUD (SCID) ($n = 20$); female ($n = 9$); male ($n = 11$) Disinterested in treatment or abstinence *M* age, 48.6 y	I: subanaesthetic ketamine infusion (0.71 mg/kg i.v.) C: midazolam (0.025 mg/kg)	Cocaine self-administration (choice: cocaine or monetary reward; baseline and 28 h post infusion); cocaine use in natural ecology ($ spent in natural ecology; baseline and thrice weekly for 2 weeks);	Ketamine led to lower cocaine choices at 28 h post infusion ($P < 0.0001$); significant reduction in cocaine use spending following ketamine vs. midazolam ($P < 0.05$), effect subsided after

TABLE 2 (Continued)

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
				cocaine craving (VAS); 24 h post ketamine-infusion and thrice weekly for 2 weeks)	several days; significant reduction in craving before discharge following ketamine vs. midazolam ($P < 0.01$), effects subsided at follow-up time points
Dakwar *et al*., 2018 [71], USA	RCT (inpatient, hospitalised)	Diagnosed CoUD (*n* = 18); female (*n* = 8); male (*n* = 10) Disinterested in treatment or abstinence *M* age, 49.8 y	I: infusion of ketamine (0.71 mg/kg i.v.) C: midazolam (0.025 mg/kg)	GIS (cocaine self-administration; cocaine use in natural ecology and cocaine craving) from baseline to 2 weeks post-treatment	Ketamine was associated with significantly GIS scores vs. midazolam ($P < 0.001$)
Dakwar *et al*., 2019 [35], USA	RCT (inpatient infusion/ outpatient psychosocial intervention)	Diagnosed CoUD (DSM-IV) (*n* = 55); female (*n* = 14); male (*n* = 41) Minimum cocaine use 4 weeks preceding screening *M* age, 47 y	I: ketamine infusion (0.5 mg/kg i.v.) (*n* = 27) C: midazolam (0.025 mg/kg) (*n* = 28) Combined with MBRP (*n* = 55)	Abstinence (final 2 weeks of study; urine toxicology) (6 month follow up; telephone interview); relapse (relapse or drop out); cocaine use (weekly; weeks 2–5; TLFB); craving VAS (weekly; weeks 1–5)	Abstinence: ketamine 13/27; midazolam 3/28; ketamine group had 6× odds of abstinence ($P = 0.02$) Abstinence 6 months; ketamine 12/27; midazolam 0/28 ($P < 0.001$) Relapsed: ketamine 15/27; midazolam 26/28 Ketamine group was 53% less likely to relapse vs. midazolam group ($P = 0.03$); greater odds of cocaine use after midazolam vs. ketamine ($P = 0.01$); cravings scores were 58.1% lower in ketamine group vs. midazolam group ($P = 0.01$)

(Continues)

TABLE 2 (Continued)

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
Ketamine–CaUD					
Azhari *et al*., 2021 [70], USA	Single-blind proof-of-concept trial (outpatient)	CaUD (DSM-IV-TR diagnosis) (*n* = 8); female (*n* = 4); male (*n* = 4) Age, 24–57 y	I: sub-anaesthetic ketamine infusion (0.11 mg/kg bolus, followed by 0.6 mg/kg over 50 mins; *n* = 8), with some receiving second ketamine infusion (*n* = 3) Combined with MET + MBRP (*n* = 8)	Abstinence: cannabis-using days per week (TLFB) at baseline, 7 days after 1st infusion and 7 days before end of study; craving (VAS-C) and DCQ at baseline, 24 h after 1st infusion and EOS (week 6)	Abstinence; 6/8 significantly lower avg. use days per week from baseline (B = 5.1) to 7 days after 1st infusion (B = 0.8) remaining significant until the end of the study (B = 0.5); significantly higher DCQ score from baseline (44.7) to 87.5 at the end of the study; no significant differences were found for craving
Ibogaine–OUD					
Brown and Alper, 2018 [42], Mexico	Prospective observational study (inpatient/ outpatient follow up)	OUD (DSM-IV) seeking treatment (*n* = 30); female (*n* = 5); male (*n* = 5) *M* age, 29 y	I: ibogaine test dose (3 mg/kg), followed by a flood dose (12 mg/kg) 2–12 h later (*n* = 30); booster dose (3–5 mg/kg) administered in some cases at 1–16 h post-flood dose	Addiction severity: ASIC at baseline, and 1, 6 and 12 months; opioid free days (of previous 30) at baseline and 1, 3, 6, 9 and 12 months; no. reporting no opioid use in previous 30 days at baseline and 1, 3, 6, 9 and 12 months	Decreased ASIC drug use score vs. baseline up to 12 months ($P < 0.001$); increased opioid-free days in the last 30 vs. baseline (*MD*) up to 12 months (−16.3) No opioid use in previous 30 days as follows: 50% at 1 month; 33% at 3 months; 0% at 6 months; 37% at 9 months; and 23% at 12 months
Noller *et al*., 2018 [72], New Zealand	Prospective observational study (inpatient/ outpatient follow up)	Treatment seekers for OUD (*n* = 14); female (*n* = 7); male (*n* = 7) Age, 28–47 y	I: staggered ibogaine doses (25–55 mg/kg; oral) over 24–96-h; test dose of 200 mg given post-withdrawal, followed by a larger dose 1–4 h later (400–600 mg); smaller doses then given in rapid succession (200 mg, 20-min intervals) until	ASI-Lite at baseline and 12 months; reduction in substance use in participants remaining at 12 months; no. reporting opioid use in previous	Decrease in ASI-Lite drug subscale ($P < 0.01$); reported opioid use in previous 30 days: 3 months: 43%; 6 months: 50%; 12 months: 45%

TABLE 2 (Continued)

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
			provider determined the appropriate level of dosing had been reached	30 days 3, 6 and 12 months	
Mash *et al*., 2000 [73], USA	Open-label trial (inpatient)	DSM-IV diagnosis OUD (*n* = 27); female (*n* = 4); male (*n* = 23) *M* age, 34.6 y	I: ibogaine (500 mg, 600 mg or 800 mg)	HCQN-29	Those undergoing opiate detox showed significantly decreased drug craving for all subscales at 36 h post-treatment ($P < 0.001$), and this persisted at program discharge
Ibogaine–CoUD					
Prior and Prior, 2014 [74], Brazil	Double-blind, controlled study (inpatient/ outpatient follow up)	Cocaine use least once weekly, and DSM-IV-TR diagnosis (*n* = 20); male only Age, 18–64 y	I: 1800 mg dried extract of ibogaine (75% pure) C: placebo capsule of sugar powder Biweekly consultations with psychiatrist up to 24 weeks after treatment completion	Craving for cocaine (MCCS) Urine test for cocaine over 24 weeks	Significantly improved craving scores within ibogaine group 72 h ($P < 0.0001$) to 24 weeks post-exposure ($P = 0.0047$); significant difference in craving scores for ibogaine vs. placebo at 72 h and 24 weeks ($P < 0.0001$); significantly lower rate of positive drug test results in ibogaine group vs. placebo group ($P = 0.023$) at 24 weeks
Mash *et al*., 2000 [73], USA	Open-label trial (inpatient)	DSM-IV diagnosis of CoUD (*n* = 27); female (*n* = 4); male [23] *M* age, 37.5 y	I: ibogaine (500 mg, 600 mg or 800 mg)	CCQN-45	Significantly decrease in craving was seen in 3/5 subscales (anticipation of positive outcomes ($P = 0.05$), relief of negative states ($P = 0.0005$), lack of control ($P = 0.002$)

(Continues)

TABLE 2 (Continued)

Author (date), country	Design (setting)	Participants (*n*)	Interventions	Outcome measures (follow-up)	Efficacy
Ibogaine–PSUD					
Schenberg *et al*., 2014 [46], Brazil	Retrospective observational study (private residential clinic)	PSUD (DSM-IV); alcohol, cannabis, cocaine, opioids and methamphetamine; polysubstance; (*n* = 75); female (*n* = 8); male [61]	I: multiple ibogaine sessions + CBT (17 mg/kg oral)	Abstinence at contact with researchers (%); duration of abstinence; relapse (*n*/total); adverse reactions	Abstinence: 61% of pts reached abstinence; median 5.5 months after 1 session increasing to 8.4 months with multiple sessions ($P < 0.001$) Relapse rates; session 1, 55/75 pts; session 2, 18/36 pts; session 3, 6/14 pts; session 4, 4/5 pts; session 5, 1/2 pts
MDMA–AUD					
Sessa *et al*., 2021 [75], UK	Open-label trial (outpatient)	AUD diagnosis (DSM-IV) (*n* = 14); female (*n* = 6); male (*n* = 8) *M* age, 48 y	I: 8-weeks recovery-based therapy (10 psychotherapy sessions), consisting of MI and CBT approaches; session 3 and 7 patients received MDMA during a 6- to 8-hour assisted therapy session Initial dose (125 mg oral) + booster after 2 h (62.5 mg oral)	Changes in drinking behaviour (TLFB; units/week pre-detox, at detox and 1-, 2-, 3-, 6- and 9-months post-detox); adverse effects	Abstinence at 9 months; 9/14 total abstinence 2/14 drinking fewer than 14 units; 3/14 relapsed

Note: Studies that used the same sample have been identified. Where appropriate significant values have been provided.
Abbreviations: ASIC, ASI-composite; ASI-Lite, Addiction Severity Index-Lite; AUD, alcohol use disorder; C, control; CaUD, cannabis use disorder; CCQN-45 Cocaine Craving Questionnaire; CoUD, cocaine use disorder; DCQ, Drug Taking Confidence scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; GIS, Global improvement score; HCQN-29, Heroin Craving Questionnaire; I, intervention; i.m: intramuscular; KPT, ketamine psychedelic therapy; LSD, d-lysergic acid diethylamide; *M*, mean; MCCS, Minnesota cocaine craving scale; *MD*, mean difference; MET, motivational enhancement therapy; MDMA, 3,4-methylenedioxymethamphetamine; OUD, opioid use disorder; PE, psychoeducation; PT, psychotherapy; PSUD, polydrug-SUD; pts, participants; SUD, substance use disorder; TLFB, timeline follow back; TAU, treatment as usual; UK, United Kingdom; URICA, University of Rhone Island Change Assessment; USA, United States of America; VAS, Visual Analogue Scale.

Classic psychedelics

LSD

There were 13 studies for AUD [18–24, 62–67] and one RCT study for OUD [25]. Eight were RCTs with 720 participants [22–25, 62, 65–67], five were open label clinical trials with 211 participants [18–21, 63] and one was a non-randomised controlled study with 125 participants [64]. The AUD studies used single and multiple doses of LSD (range: 200–400 mcg). Period of abstinence (defined as no alcohol consumed during follow-up) was the typical outcome. A few studies allowed occasional very low-level drinking episodes in what was classified as complete abstinence. Various definitions of reduced drinking were used. In comparison with control groups, four studies reported that LSD was associated with a significant increase in abstinence and a significant decrease in alcohol use [22, 24, 64, 66].

Five of 13 studies reported no significant differences on alcohol outcomes between LSD and controls [22, 23, 62, 65, 67]. Three of 13 studies assessed AUD relapse. In two studies, one patient relapsed [18, 64]. In the Ludwig *et al*. study, 65% of participants relapsed by 3 months and this rate increased to 80% to 90% by 12 months [23].

TABLE 3 Evaluation of risk of risk of bias for RCTs of classic and non-classic psychedelics for SUD (Cochrane risk-of-bias tool; RoB 2.0).

Study	Psychedelic	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall RoB
Classic							
Smart *et al.* 1966 [66]	LSD	Low	Some concerns	Low	Low	Some concerns	Some concerns
Hollister *et al.* 1969 [22]	LSD	Low	Some concerns	Some concerns	Low	Some concerns	High
Ludwig *et al.* 1969 [23]	LSD	Low	Some concerns	Low	Low	Some concerns	Some concerns
Johnson *et al.* 1969 [64]	LSD	Low	Some concerns	Low	Low	Some concerns	Some concerns
Bowen *et al.* 1970 [61]	LSD	Low	Some concerns	High	Low	Some concerns	High
Pahnke *et al.* 1970 [65]	LSD	Low	Some concerns	High	Low	Some concerns	High
Tomsovic and Edwards 1970 [24]	LSD	Low	Some concerns	Low	Low	Some concerns	Some concerns
Savage and McCabe 1973 [25]	LSD	Low	Some concerns	Low	Low	Some concerns	Some concerns
Bogenschutz *et al.* 2022 [37]	Psilocybin	Low	Some concerns	Low	Some concerns	Low	Some concerns
Non-classic							
Dakwar *et al.* 2014 [43]	Ketamine	Low	Some concerns	Low	Low	Some concerns	Some concerns
Dakwar *et al.* 2017 [44]	Ketamine	Low	Some concerns	Low	Low	Some concerns	Some concerns
Dakwar *et al.* 2018 [71]	Ketamine	Low	Some concerns	Low	Low	Some concerns	Some concerns
Dakwar *et al.* 2019 [35]	Ketamine	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Dakwar *et al.* 2020 [69]	Ketamine	Low	Some concerns	Low	Low	Some concerns	Some concerns
Grabski *et al.* 2022 [36]	Ketamine	Low	Low	Low	Low	Low	Low
Krupitsky and Grinenko 1997 [28]	Ketamine	High	Some concerns	Some concerns	Low	Some concerns	High
Krupitsky *et al.* 2002 [40]	Ketamine	Low	Some concerns	Low	High	Some concerns	High
Krupitsky *et al.* 2007 [41]	Ketamine	Low	Some concerns	Low	Low	Some concerns	Some concerns

Note: Overall RoB judgement: Low, there are no concerns of risk of bias in any domain. Some concerns, there are some concerns of risk of bias in one or more domains, but no high risk of bias in any domain. High, there are concerns of a high risk of bias in one or more domains, or some concerns of risk of bias in several domains.

Abbreviations: LSD, d-lysergic acid diethylamide; RoB, risk of bias; SUD, substance use disorder.

In the single OUD study by Savage and McCabe [25] using a single dose of LSD (range: 200–500 mcg), 12 of 37 participants achieved 12 months of abstinence compared with two participants in the control group [25]. Three of 12 participants relapsed, but they each subsequently achieved at least a year of abstinence.

Mescaline

There was one study for AUD. This was an open-label element of Smith *et al.*'s [18] study of LSD. Seven participants received mescaline: three achieved abstinence, two had improved AUD and two did not change.

TABLE 4 Cochrane RoB tool for ROBINS-I for classic psychedelics.

Study name	Bias because of confounding	Bias because of the selection of participants	Bias because of the classification of interventions	Bias because of deviations from intended interventions	Bias because of missing data	Bias because of the measurement of outcomes	Bias because of the selection of reporting results	Overall RoB judgement
Smith *et al.* 1958 [18]	Serious	Serious	Low	NI	Low	Serious	Moderate	Serious
Jensen and Ramsay, 1963 [63]	Serious	Serious	Moderate	NI	Serious	Serious	Serious	Serious

Note: Overall risk of bias judgements for serious were achieved as directed by Cochrane's definition of serious risk of bias (the study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain).
Abbreviations: Critical, the study is too problematic to provide any useful evidence on the effects of intervention; Low, the study is comparable to a well performed randomised trial regarding this domain; Moderate, the study is sound for a non-randomised study regarding this domain but cannot be considered comparable to a well performed randomised trial; NI, no information on which to base a judgement on; RoB, risk-of-bias; ROBINS-I, RoB in non-randomised studies of interventions.

TABLE 5 Grades of recommendations, assessments, development and evaluations for RCTs.

Outcome	Effect	No. of participants	Certainty in evidence
Classic psychedelics			
LSD for AUD: abstinence	Most studies found mixed findings for the effect on abstinence.	*n* = 646 (7 RCTs)	Very low (because of very serious ROB and serious inconsistencies[a])
LSD for AUD: relapse	Relapse ranged from 65%–90% across all treatment groups at 3–12 months	*n* = 176 (1 RCT)	Very low (because of serious ROB and very serious inprecision[b])
Psilocybin for AUD: abstinence	There was a significant reduction in percentage of heavy drinking days at follow-up	*n* = 95 (1 RCT)	Moderate (because of serious rating for imprecision[c])
Non-classic psychedelics			
Ketamine for AUD: abstinence	Ketamine was associated with significantly greater abstinence vs. controls	*n* = 375 (3 RCTs)	Low (because of serious ROB and serious imprecision[d])
Ketamine for AUD: relapse	Ketamine was associated significantly lower relapse rates vs. controls	*n* = 375 (3 RCTs)	Low (because of serious ROB and serious imprecision[d])
Ketamine for CoUD: abstinence	Ketamine was associated with a significant reduction in cocaine use and improved abstinence	*n* = 64 (3 RCTs)	Very low (because of serious ROB and very serious imprecision[e])
Ketamine for CoUD: craving	Ketamine was associated with a significant reduction in craving	101 (4 RCTs)	Very low (because of serious ROB and very serious imprecision[e])
Ketamine for OUD: abstinence	High/multiple dose ketamine was associated with significantly increased abstinence vs. low dose/single dose ketamine	*n* = 123 (2 RCTs)	Low (because of serious ROB and serious imprecision[f])
Ketamine for OUD: craving	Multiple ketamine was associated with a significant reduction in craving vs. single dose ketamine	*n* = 123 (2 RCTs)	Low (because of serious ROB and serious imprecision[f])

Abbreviations: AUD, alcohol use disorder; CoUD, cocaine use disorder; LSD, d-lysergic acid diethylamide; n, number of study participants; OUD, opiod use disorder; n, number of study participants; RCT, randomised controlled trial; ROB, risk of bias.
[a]There is inconsistency in the outcome abstinence for LSD for AUD as several studies reported significant effects whilst others reported no significant impact between LSD and controls.
[b]Only one study was assessed with 176 participants, with no CIs reported to support the estimate.
[c]The total number of participants does not meet the threshold for precision criteria to determine an effect on the outcome.
[d]There was a low number of participants to determine an effect on the outcome. This was judged as "serious" and not "very serious" because CIs were reported for abstinence and relapse measures.
[e]Extremely low sample size for the combined studies, with only one study reporting CIs.
[f]The total number of participants does not meet the threshold for precision criteria to determine an effect on the outcome.

Psilocybin

There were two studies for TUD, an open-label clinical trial with 15 participants [38] and a longer-term follow up by Johnson *et al*. [39] of the same participants. In the TUD study, psilocybin was given three times (dose: 20–30 mg per 70 kg body weight) alongside six individual and group psychotherapy sessions. At 6-month and 12-month follow-up, 12 of 15 participants reported biologically verified abstinence from smoking. At longer-term follow-up (mean 30 months), nine of 15 participants were abstinent.

There were two studies for AUD, a proof-of-concept feasibility trial with 10 participants Bogenschutz *et al*. [34], and a two-centre, double-blind, phase 2 superiority RCT with 95 participants Bogenschutz *et al*. [37]. In the latter study, 49 participants were assigned to receive psilocybin (25 mg per 70 kg) and 46 participants received diphenhydramine (a sedating antihistamine; 25–40 mg per 70 kg) after 4 and 8 weeks of motivational enhancement therapy (MET) [37]. There were significant group differences in the change from baseline to week 32 in favour of psilocybin for the number of heavy drinking days (mean difference, 13.86), the percentage of drinking days (mean difference, 13.44%) and the number of drinks per drinking day (mean difference, 1.09).

Ayahuasca

There were three observational clinical studies for people with various mono and dual SUDs including AmUD, AUD, CaUD, CoUD, OUD and 'tranquiliser use disorder' [45, 61, 68] among 101 participants. Ayahuasca was given as part of a multi-modal psychosocial intervention that included counselling, psychotherapy, relapse prevention and psychodrama [68]. Berlowitz *et al*. [61] and O'Shaughnessy *et al*. [68] reported significant improvements in substance craving in the ayahuasca group. Thomas *et al*. [45] reported reductions in alcohol, cocaine and tobacco use. In the Berlowitz *et al*. [61] study only CoUD outcomes (reduced drug use and 'addiction severity') were significantly associated with ayahuasca.

Non-classic psychedelics

Ketamine

There were three studies for AUD [28, 36, 69], one study for CaUD [70], four studies for CoUD [35, 43, 44, 71], and two studies for OUD [40, 41]. Nine of 10 studies were RCTs among 571 participants [28, 35, 36, 40, 41, 43, 44, 69, 71]. The final study was a proof-of-concept feasibility study [70].

In the three AUD trials, a single dose of ketamine was given to 347 participants (dose range: 0.71–2.5 mg per kg body weight). In the Krupitsky and Grinenko [28] and Dakwar *et al*. [69] studies, midazolam and treatment as usual (TAU) were the control conditions, and all participants were offered group psychotherapy [28] and MET [69]. Grabski *et al*. [36] conducted a two-centre, double-blind, four-arm, placebo-controlled phase 2 RCT to contrast intravenous ketamine with a saline infusion; psychotherapy with saline infusion; ketamine and alcohol education; and saline infusion and education.

Across all three studies, the ketamine assigned groups achieved more abstinence. Dakwar *et al*. [69] reported that 75% of the ketamine group were abstinent compared with 27% in the control group, with a longer time to any relapse in the ketamine group. At 6-month follow-up, Grabski *et al*. reported a mean difference of 10.1 for abstinence compared with controls. In the Krupitsky and Grinenko study [26], there was a significant ketamine effect at 12-month follow-up compared with TAU.

In the OUD trials, Krupitsky *et al*. [40] compared ketamine (2 mg per kg body weight) with low dose ketamine alongside psychotherapy in 70 participants. In a follow-up, Krupitsky *et al*. [41] evaluated single or multiple doses of ketamine in 53 participants. Ketamine was associated with significantly increased abstinence and decreased opioid craving at 12-month follow-up, with these outcomes maintained at 24-month follow-up [40].

In four CoUD RCTs by Dakwar *et al*. [35, 43, 44, 71], ketamine was administered at varying doses (ranging from 0.41 mg/kg to 0.71 mg/kg) to a total of 101 participants. Lorazepam and midazolam were used as the control conditions in three studies [35, 43, 44]. One study included 'mindfulness-based behavioural modification' [35]. Craving and cocaine use were the common outcome measures. In all studies, ratings of cocaine craving after ketamine were significantly lower 2 to 5 weeks after infusion [35, 43, 44, 71]. Dakwar *et al*. [44] reported that this short-term effect attenuated at later follow-up. All studies reported a significant reduction in cocaine use [35, 43, 44, 71]. In one study there remained a significantly higher rate of cocaine abstinence at 6 months [35].

In the CaUD study, Azhari *et al*. [70] administered a single sub-anaesthetic ketamine infusion (0.11 mg/kg followed by 0.6 mg/kg over 50 minutes) to eight participants. Three participants received a second infusion adjunctive to MET and mindfulness-based relapse prevention. Compared with baseline, the number of use days per week decreased at follow-up, with reductions in craving reported immediately after infusion, however, this was not significant.

Ibogaine

There were two observational studies for OUD with 44 participants [42, 72], one open label study for OUD and CoUD with 27 participants [73], one double-blind RCT for CoUD with 20 participants [74], and one retrospective observational study for PSUD with 75 participants [46].

In the observational OUD studies Brown and Alper [42] and Noller *et al*. [72], participants received multiple doses of ibogaine (3–12 mg/kg) [42] and (25–55 mg/kg) [72]. There was a significant reduction in OUD severity at 12 months [42] and an increase in opioid abstinence in the past 30 days at 12-month follow-up [42]. In Mash *et al*.'s open-label study, participants with either OUD or CoUD

received multiple doses of ibogaine (500–800 mg) [73] with a significant reduction in opioid and cocaine craving outcomes. In the RCT CoUD trial by Prior and Prior [74], participants were randomly allocated to receive ibogaine (1800 mg) or placebo with immediate outcome assessment and a 24-week follow-up. There was a significant (positive) difference in craving scores between ibogaine and placebo groups 72 hours post-dosing and at 24-week follow-up. There was a significantly lower rate of positive cocaine drug test results in the ibogaine group compared with the placebo group.

The PSUD retrospective observational by Schenberg *et al.* [46] followed 75 participants of whom 54 had problematic use of alcohol, cannabis, cocaine, opioids and amphetamines. Ibogaine was dosed on average 17 mg/kg and was administered alongside a programme of cognitive behavioural therapy (CBT). Abstinence was reported by 61% of participants. Individuals receiving a single dose of ibogaine had an abstinence median period of 5.5 months compared to 8.4 months for those who received the treatment multiple times.

MDMA

There was an open label study for AUD by Sessa *et al.* [75] with 14 participants. MDMA was administered over two sessions (125 mg then a 'booster' of 65 mg). The participants were offered an 8-week (10 session) course of 'recovery-oriented psychotherapy' based on motivational interviewing and CBT [75]. Reduced alcohol use was reported at 1-month and 9-month follow-up reducing to 18.7 units from 130.6 pre detox.

RoB

Table 3 shows the RoB evaluation for the eight LSD, one psilocybin and nine ketamine RCTs. We rated six of the LSD studies with some concerns and two with high RoB because of missing outcome data. Bogenschutz *et al.*'s psilocybin RCT was rated with some concerns because participants were aware of their allocated intervention and potential bias among unblinded outcome assessors [37]. For ketamine, the Grabski *et al.* [36] RCT was rated with a low RoB. The Dakwar *et al.* [35, 43, 44, 69, 71] trials were rated with some concerns because of deviations from the intended intervention and apparent selection of findings. Two of three Krupitski *et al.* [26, 38] trials were judged to have high RoB and the other with some concerns. Table 4 summarises our ROBINS-I rating of serious RoB for the two non-randomised trials of classic psychedelics [18, 64]. The observational studies on ayahuasca and ibogaine and the open-label study of MDMA were not ROBINS-I rated because they lacked a no-drug comparator.

Overall quality of evidence

Table 5 shows our overall evaluation of the pooled evidence of SUD efficacy from RCTs. We rated the evidence certainty for the LSD RCTs very low–low, because of very serious RoB and inconsistencies in abstinence outcomes and serious RoB and imprecision for relapse outcomes. We judged there was moderate evidence certainty from the single trial of psilocybin-AUD abstinence outcomes because there was no serious RoB, nor any inconsistencies or indirectness in outcome measurement. We judged that there was very low–low evidence certainty for all ketamine studies because of very serious RoB (i.e. some concerns–high RoB), and outcome imprecision (i.e. small samples yielding wide estimates).

DISCUSSION

In this pre-registered systematic review, we identified 37 studies of psychedelic-assisted treatment for SUD, with a total of 2035 participants. There was no SAE reported in any of the reviewed articles, but only 38% of the studies reported on safety. It is unknown if safety data was recorded, but not reported.

A substantial proportion of the literature related to early studies of LSD for AUD (13 RCTs with 720 participants). As one would expect, these studies were not conducted to contemporary standards of methodological quality, and we conclude there is very low–low evidence certainty and very serious RoB for LSD at this point. The ketamine studies for AUD, CaUD, CoUD and OUD (nine RCTs with 571 participants), and the early phase study of psilocybin for TUD, all provide low evidence certainty, but they do lend progression support for larger studies. In our judgement, there are two best conducted studies in the SUD field to date: Bogenschutz *et al.*'s two-centre, double-blind, phase 2 RCT of psilocybin for AUD [37] and Grabski *et al.*'s two-centre, double-blind, four-arm, placebo-controlled phase 2 RCT for AUD [36]. Our conclusions regarding evidence quality and RoB are certain to change in the light of the many studies underway.

This review has some strengths. It was pre-registered followed established guidelines for systematic reviews, and it achieved some consistency in the tabulation of findings on efficacy. The review was not easy to conduct given differences in psychedelic drug administration and the type and intensity of psychosocial interventions offered to participants.

In setting out our recommendations for future studies, it is axiomatic that RCTs must be registered and adhere to the appropriate Consolidated Standards of Reporting Trails (CONSORT) guideline, and good practice principles (i.e. the Declaration of Helsinki [76], and Guidelines for Good Clinical Practice [77]).

Reporting and evaluating safety events

A requirement to fully report safety events seems hardly necessary to state. This review included studies conducted at a time before standardisation of safety event reporting and classification. However, we note that a systematic review in 2023 of adverse events reported in RCTs of eskatamine for major depressive disorder found that 42% of

SAEs and 39% of non-SAE were not reported in published articles on efficacy [78].

The risk of misuse in classic psychedelics appears to be low [12, 13]. Although concerns have been raised about the addictive nature of ketamine, to our knowledge there have been no reports of index ketamine use disorder after a treatment study [50]. An intense cognitive-affective experience is expected in a psychedelic dosing session, but it should not be expected that participants can provide a detailed account afterward. The emotional valence of a psychedelic experience may change as well (i.e. an experience during dosing that is reported as distressing, is later viewed positively and vice versa). Traditional safety event recording procedures do not seem entirely suitable for psychedelic-assisted treatment studies. To assist the field, safety monitoring instruments [79] and a standardised framework for assessing adverse events of special interest in psychedelic-assisted treatment trials have been developed [80].

Inclusion and exclusion criteria

Less is known about the typical inclusion and exclusion criteria that should be used in this field than elsewhere in SUD pharmacotherapeutics. The outcome goal (e.g. complete abstinence or avoidance of harmful drinking levels) and required status of the participant (e.g. completion of medically supervised withdrawal) would help in the evaluation of study findings and their generalizability. More needs to be known about the characteristics that would make a psychedelic contraindicated for a person who is interested in participating in a treatment trial. Some people (including those with co-morbid stress and mood disorders) may find a psychedelic experience extremely unpleasant or distressing [78, 81].

Blinding

The design of clinical trials involving psychedelic (and indeed all strongly psychoactive) drugs inherently conflicts with established paradigms of trial design that seek the blinding of participants to study interventions and the balancing of expectancy effects between groups. The potentially profound effects of a psychedelic on consciousness, self-perception and emotion means there is little chance that a participant would not be aware of their assigned condition. Assigning participants to an active comparator can be done (diphenhydramine for psilocybin and midazolam for ketamine to give two examples in this review) but can remain qualitative differences in effect that mean blinding is not achieved (e.g. in Bogenschutz *et al.*'s [37] study, 95% of participants and their therapists correctly guessed the random allocation). There may be some options to mitigate, including blinded raters and analysts, and the pragmatic solution to use a low dose of the target psychedelic and offer responder participants the experimental condition dose in an open-label extension may reduce treatment allocation despondency and study withdrawal.

Design

Given complexity of effects, factorial designs for RCTs may be an optimal means of analysis (e.g. a psychedelic and a psychosocial intervention with their comparators). An extension to CONSORT has recently been published to guide these designs [82]. This would be an efficient means of testing each psychedelic and psychosocial factor and their combination. This design would also work for the investigation of a psychedelic with another (e.g. psilocybin versus ketamine) with all participants receiving a standard psychosocial intervention. Although factorial designs are efficient two-for-one studies, they are larger-scale and costly of resources than simple head-to-head trials and they may be challenging to analyse and interpret.

Outcome measures

Different research groups have their preferences for using continuous (e.g. a count of abstinent days or negative biomarker tests) or binary outcomes (e.g. no use of substance in the final days of the treatment period or whether the participant achieves a period of sustained abstinence) will doubtless continue. The former approach may be advantageous because is captures more data and is more statistically powerful, and because there can be unfortunate limitations with a binary response outcome because: (a) a participant who responds well right up to the final classifying stage of the treatment period, but then lapses, is taken to have not responded at all to treatment which is insensitive; and (b) a participant who achieves the defined a period of sustained abstinence early on, but then lapses, is taken to be a treatment responder even if they are no longer abstaining at the endpoint. The psychedelic-assisted treatment for SUD field could benefit from a core outcome set, as promoted by the COMET initiative [83], where standardised measures are set out and are reported in all publications to facilitate reporting and meta-analysis. A Delphi consensus initiative could address this need for the field.

Fidelity assurance and pre-registered analyses and fidelity assurance

It is standard practice in the addictions treatment field to use manual-guided therapies, with appropriately competent and trained practitioners, and with fidelity monitoring. This approach should be followed here with recording of dosing and therapy sessions. Study protocols must be available, and all major amendments that affect the statistical analysis plan must be reported. The best studies will pre-register their statistical analysis plans before the dataset is locked. Several pre-registered sensitivity analyses should be done on the primary outcome measure. Repeating the adjusted primary outcome model with the addition of subgroups (e.g. whether the participant has prior experience of psychedelics and whether they have used a psychedelic drug outside the protocol after randomisation) can evaluate whether the factor is prognostic and should be a stratification factor in future. A mixed

set of approaches to investigate efficacy on RCTs is also suggested, including phenomenological qualitative studies, secondary analyses of effect mediation, and neuroimaging studies of the hypothesised action of psychedelics (e.g. modulation of networks and connectivity [84]).

CONCLUSION

In this narrative review, the best evidence for SUD treatment efficacy is psilocybin and ketamine for AUD. The early phase study of psilocybin for TUD, and the RCTs of ketamine for AUD, CaUD, CoUD and OUD constitute low evidence certainty, but provide progression rationale for larger studies (with findings from future studies likely to change our current evaluation). Future research should: report all safety events using appropriately adapted procedures; better screen for person-level characteristics that indicate that psychedelic-assisted SUD treatment is contraindicated; strive to mitigate blinding of participants to interventions; use factorial designs for psychedelic and psychosocial RCTs; and build consensus for a field-specific core outcome set to promote standardisation and meta-analysis.

AUTHOR CONTRIBUTIONS

Theodore Piper: Conceptualization (equal); formal analysis (equal); methodology (equal); project administration (equal); writing—original draft (equal). **Francesca Small:** Investigation (equal); methodology (equal); project administration (equal); writing—original draft (equal). **Sam Brown:** Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); writing—original draft (supporting). **Michael Kelleher:** Writing—original draft (supporting). **Luke Mitcheson:** Writing—original draft (supporting). **James Rucker:** Writing—original draft (supporting). **Allan H. Young:** Writing—original draft (supporting). **John Marsden:** Conceptualization (equal); methodology (equal); writing—original draft (equal).

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DATA AVAILABILITY STATEMENT

This was a systematic review.

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