Impact of psychedelics on craving in addiction: A systematic review

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SC, MA, AGR designed the study. SC, GB, JDT, LDL, CL, independently selected the studies and extracted the data by groups of two. Discrepancies were resolved by MN. SC drafted the first version of the manuscript. BS, RD and AGR provided expertise on psychedelic therapy. MN, FS and BR provided expertise on systematic review and meta-analysis. All authors significantly contributed to the manuscript and approved the final version.

Funding:
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 04.18.2021 (registration number CRD42021242856).

Number of Words: 220 (Abstract), 5752 (Main text)
Number of Tables: 2
Number of Figures: 2
Number of Supplements: 3

ABSTRACT

Background: In the context of the need to increase treatment options for substance use disorders, recent research has evaluated the therapeutic potential of psychedelics. However, there is an incomplete understanding of psychedelics' effects on craving, a core symptom of addictive disorders and a predictor of substance use and relapse.

Aims: To determine if use of psychedelics is associated with changes in craving in humans.

Methods: A systematic review of the literature, using PubMed, PsycInfo, and Scopus databases up to May 2023. We included all studies assessing any substance craving levels after psychedelic use (protocol registration number CRD42021242856).

Results: Thirty-eight published articles were included, corresponding to 31 studies and 2,639 participants, pertaining either to alcohol, opioids, cocaine, or tobacco use disorders. Twelve of the 31 included studies reported a significant decrease in craving scores following psychedelic use. All but two studies had methodological issues, leading to moderate to high risk of bias scores.

Conclusions: Some psychedelics may show promising anti-craving effects, yet the diversity and high risk of bias of extant studies indicate that these results are to be considered with caution. Further well-controlled and larger-scale trials should be encouraged.

Declaration of interests: The authors declare that there is no conflict of interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Keywords: Psychedelics; hallucinogens; craving; addiction; use disorder; systematic review.

INTRODUCTION

Addiction is a chronic-relapsing condition characterized by a loss of control over the use of a rewarding substance or behavior despite negative consequences (American Psychiatric Association, 2013; Auriacombe et al., 2018; Hasin et al., 2013). In 2015, 6.4 million global deaths were attributed to smoking with a prevalence of smoking of 25% for men and 5.4% for women (Reitsma et al., 2017). In 2016, there were also 100.4 million estimated cases of alcohol, 22.1 million of cannabis and 26.8 million of opioid use disorders worldwide, leading to 2.8 million deaths attributed to alcohol use and 452 000 to other substance use (Degenhardt et al., 2018). Furthermore, the current opioid crisis in North America constitutes a primary public health concern in need of new medications (Volkow and Blanco, 2021), for which psychedelic substances could be candidates (Argento et al., 2019b).

Many studies have highlighted the clinical significance of craving in the maintenance and treatment of addictions (Skinner and Aubin, 2010; Tiffany and Wray, 2012; Serre et al., 2015; Weiss, 2005). Craving can be defined as "the subjective experience of wanting to use a substance" (Tiffany and Wray, 2012), often described as intense, compelling (Rosenberg, 2009), and unwanted (Serre et al., 2015; Auriacombe et al., 2018). It involves emotional, cognitive, physiological and behavioral components, having notably been associated with a wide range of emotional (such as anxiety and irritability) and physiological reactions (such as increased salivation, skin conductance, heart rate and blood pressure) (Rosenberg, 2009; Skinner and Aubin, 2010). Craving has been identified as a major predictor of substance use and relapse (Skinner and Aubin, 2010; Tiffany and Wray, 2012; Serre et al., 2015; Weiss, 2005), making it a construct at the core of addiction (Gauld et al., 2023; Auriacombe et al., 2018; Sayette, 2016) as well as a treatment target of primary interest (Sinha, 2009).

Although currently available pharmacological treatments may be effective for some patients with alcohol, opioids, and tobacco use disorders (Van den Brink, 2012; Maisel et al., 2013), they are few in

number, leaving many patients with poor prognoses and no alternatives. Consequently, there is a strong need for new medications in this field, a role some have suggested psychedelics could fill (Winkelman, 2014; Sessa, 2018; Bogenschutz and Johnson, 2016; DiVito and Leger, 2020; Dos Santos et al., 2016; Jones et al., 2018).

Psychedelics are a group of psychoactive substances that cause profound alterations of consciousness via changes in perceptual, cognitive, and affective processes (Johnson et al., 2019; Garcia-Romeu et al., 2016). The term 'psychedelic' has been applied to classic psychedelics, that operate predominantly via agonism at serotonin 2A (5-HT2A) receptors, including tryptamines such as dimethyltryptamine (DMT), psilocybin and lysergic acid diethylamide (LSD) and phenethylamines such as mescaline (Johnson et al., 2019; Garcia-Romeu et al., 2016; Bogenschutz and Pommy, 2012), to empathogens or entactogens, which are mixed serotonin and dopamine reuptake inhibitors and releasers, such as 3,4-methylenedioxy-methamphetamine (MDMA), to dissociative anesthetics, acting as N-methyl-D-aspartate (NMDA) antagonists, such as ketamine and dextromethorphan, and to atypical hallucinogens, including the indole alkaloid ibogaine (Garcia-Romeu et al., 2016). The taxonomy of psychedelics is complex. Some authors consider 'non-serotonergic psychedelics' to be a misnomer, arguing 5-HT2A agonism is necessary for the psychedelic experience (Nichols, 2016; Johnson et al., 2019), whereas others underline their shared patterns of subjective experiences and downstream pharmacological effects (Kadriu et al., 2021; Vollenweider and Kometer, 2010; Ly et al., 2018; Garcia-Romeu et al., 2016; Krupitsky and Grinenko, 1997; Schenberg, 2018). Considering this latter argument and given the current interest in these compounds as a potential treatment of addictions, we considered 'psychedelics' here by their broadest definition.

While the majority of psychedelics are currently classified as substances of abuse in most parts of the world, early and more recent findings suggest their promising potential in the treatment of addictions

(Mash et al., 1998; Winkelman, 2014; Garcia-Romeu et al., 2016; DiVito and Leger, 2020; Bogenschutz and Johnson, 2016; Sessa et al., 2021). From the 1950s to the early 1970s, over 30 trials aimed to test the efficacy of LSD in the treatment of alcohol addiction (Bogenschutz and Pommy, 2012). Two systematic reviews including some of these trials concluded that LSD held promise for the treatment of alcohol use disorder, but noted methodological concerns limiting the significance of their results (Fuentes et al., 2020; Krebs and Johansen, 2012).

Ketamine has been studied since the 1990s for the treatment of addictions, with trials mainly examining treatment potential for alcohol, cocaine and opioid use disorders (Ezquerra-Romano et al., 2018; Jones et al., 2018). Since the late 1990s, ibogaine has been increasingly used in medically monitored addiction treatment clinics in several countries, with some trials suggesting its efficacy in the treatment of opioid, alcohol, and other substance use disorders (Corkery, 2018). Ayahuasca has been primarily studied in ceremonial or ritualistic settings (Argento et al., 2019a), notably within several Brazilian churches using this compound as sacrament, such as the Santo Daime (Liester and Prickett, 2012), where it has been found to exhibit anti-addictive properties. Two recent open-label studies evaluating the efficacy of psilocybin in the treatment of alcohol (Bogenschutz et al., 2015) and tobacco (Johnson et al., 2014) use disorders opened the way to a recently completed larger scale, randomized and controlled trial (Bogenschutz et al., 2022), with findings favoring psilocybin-assisted psychotherapy. To date, only one open label trial evaluated the safety and tolerability of MDMA-assisted psychotherapy in patients with alcohol use disorder (Sessa et al., 2021).

Despite this growing body of evidence, the mechanisms of action of psychedelics in the treatment of addictions remains only partially understood (DiVito and Leger, 2020; Bogenschutz and Johnson, 2016) and little work has focused on their impact on craving. Given the putative significance of craving in the maintenance of addiction, this information would contribute to the understanding of the potential

therapeutic effects of psychedelics. Indeed, an impact on craving, particularly if temporally antecedent to more general improvements in mood and wellbeing, would support an action of these compounds on the addiction process itself. To our knowledge, there has been no review specifically focusing on the impact of psychedelics on substance craving. We therefore investigated the link between psychedelics and craving through a systematic review of the literature. In the interest of a comprehensive approach, we included studies of any substances use disorders where craving levels were assessed after the use of psychedelics in their broadest definition, regardless of setting, to provide a comprehensive synthesis of the weight of evidence from this emerging field.

The objective of this systematic review was to determine if psychedelics are associated with changes in craving in humans across clinical and non-clinical settings.

METHODS

This systematic review follows the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Page et al., 2021) (see **Supplement 1** for the PRISMA Checklist). Its protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 04.18.2021 (registration number CRD42021242856) (https://www.crd.york.ac.uk/prospero/).

Study selection criteria

Inclusion criteria for selecting studies were as follows: (a) participants: studies including individuals with any substance use disorder. Studies pertaining to adults, regardless of their age, gender, and geographic origin were selected. (b) Intervention: the use of psychedelics in their broadest definition, including classic and non-classic psychedelics (i.e., either psilocybin, DMT, LSD, mescaline, ibogaine, ketamine or MDMA), regardless of the treatment duration, the doses administered and the setting (clinical,

non-clinical, ritual, recreational). (c) Study type: included studies were either observational or interventional, qualitative, or quantitative, including randomized controlled trials (RCTs), open-label trials, longitudinal cohort or case-control studies, cross-sectional studies, case series and case reports. (d) Outcomes: the primary outcome of interest was any measure of craving whether self-report (single item and questionnaire measures), neuropsychological, or qualitative.

Animal or pediatric population studies and studies with a lack of available information on craving were excluded. Only articles in English or French were considered.

Information sources

The relevant literature was selected using headings related to psychedelics and craving from online PubMed, PsycInfo and Scopus databases up to May 13, 2023. This search was completed by searching for preprints from https://psyarxiv.com/ and for registered protocols from https://www.clinicaltrials.gov/. Reference lists of selected studies were scanned for inclusion of further studies.

Search strategy

Articles were retrieved from online PubMed, PsycInfo and Scopus databases. The search terms included “psychedelic-assisted therapy”, “Psychedelics”, “Hallucinogens”, “Psilocybin”, “N,N-Dimethyltryptamine”, “Banisteriopsis”, “Ayahuasca”, “5-MeO-DMT”, “Mescaline”, “Ibogaine”, “Lysergic Acid Diethylamide”, “Harmine”, “Bufotenin”, “Phencyclidine”, “N-Methyl-3,4-methylenedioxyamphetamine”, “2,5-Dimethoxy-4-Methylamphetamine”, “Ketamine”, “Craving”, “Inhalant Abuse”, “Marijuana Abuse”, “Alcoholism”, “Tobacco Use Disorder”, “Amphetamine-Related Disorders”, “Cocaine-Related Disorders”, “Opium Dependence”, “Morphine Dependence”, “Heroin Dependence”, “behavior, addictive”. See **Supplement 2** for the search terms used for each database.

Selection process

Reference management software ENDNOTE X9 was used to extract and manage references. Two review authors (SC and GB, LDL, JDT or CL) independently screened the titles obtained by the search. Based on titles, publications not fitting the (a), (b) or (c) inclusion criteria or endorsing exclusion criteria were excluded. Abstracts of retained studies were obtained and examined following the same process. Studies were included even though craving was not mentioned in their title and abstract. Full texts of retained studies were then obtained and examined. Even if the declared aim was not focused on exploring craving, the methods and data analysis sections were screened to identify any craving measures. A third review author solved discrepancies at every stage of the process.

Data management

Two review authors (SC and GB, LDL, JDT or CL) extracted data independently using standardized extraction sheets. Collected data included demographic information, methods, intervention details and outcomes. A third author (MN) solved disagreements.

The following variables were extracted: a) study characteristics: authors, year of publication, journal. (b) Participant characteristics: sample size, age, gender, substances used. (c) Methods: study design, setting, type of psychedelic assessed, dosage, treatment frequency and duration, control used, follow-up. (d) Outcomes: primary outcome results, craving measures, associated factors, side effects. For craving information, we accepted other wording such as “urge to use” and “desire to use”.

The primary outcome for this review was change in craving level following use of psychedelics, assessed by a craving rating scale, questions from a questionnaire or any methods, including qualitative interview. This was not necessarily the primary outcome of the included studies. The secondary outcome included the safety and tolerability: frequency, type, and severity of side effects.

Data synthesis

A systematic qualitative synthesis with information presented in the text and tables was generated to summarize and explain the characteristics and findings of the included studies.

Quality assessment

Risk of bias of individual studies

Randomized interventional studies were assessed using the Cochrane consortium "Risk of Bias" (RoB 2.0) tool (https://training.cochrane.org/resource/rob-20-webinar) (Sterne et al., 2019). Non-randomized interventional studies were assessed using the "Risk of Bias In Non-randomized Studies" (ROBINS-I) tool (https://methods.cochrane.org/methods-cochrane/robins-i-tool) (Sterne et al., 2016). Cross-sectional quantitative, case-control and cohort studies were assessed using the "Newcastle-Ottawa Scale" (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) for cohort studies (Wells et al., 2000) or for cross-sectional studies (Herzog et al., 2013). Qualitative studies were assessed using the COnsolidated criteria for REporting Qualitative research (COREQ) checklist (Tong et al., 2007). Case reports were assessed using the Consensus-based Clinical Case Reporting (CARE) checklist (Gagnier et al., 2013). The assessment of the risk of bias was performed at the outcome level.

RESULTS

Study selection

The flow chart of the selection process is presented in **Figure 1**. A total of 2,498 articles were identified. After removal of duplicates and screening based on title and abstract, 118 full texts were obtained. 38 records were included in the review, corresponding to 31 distinct studies, listed in **Supplement 3**. The agreement (Cohen's kappa) between review authors on full text selection was 0.79. Twelve reports

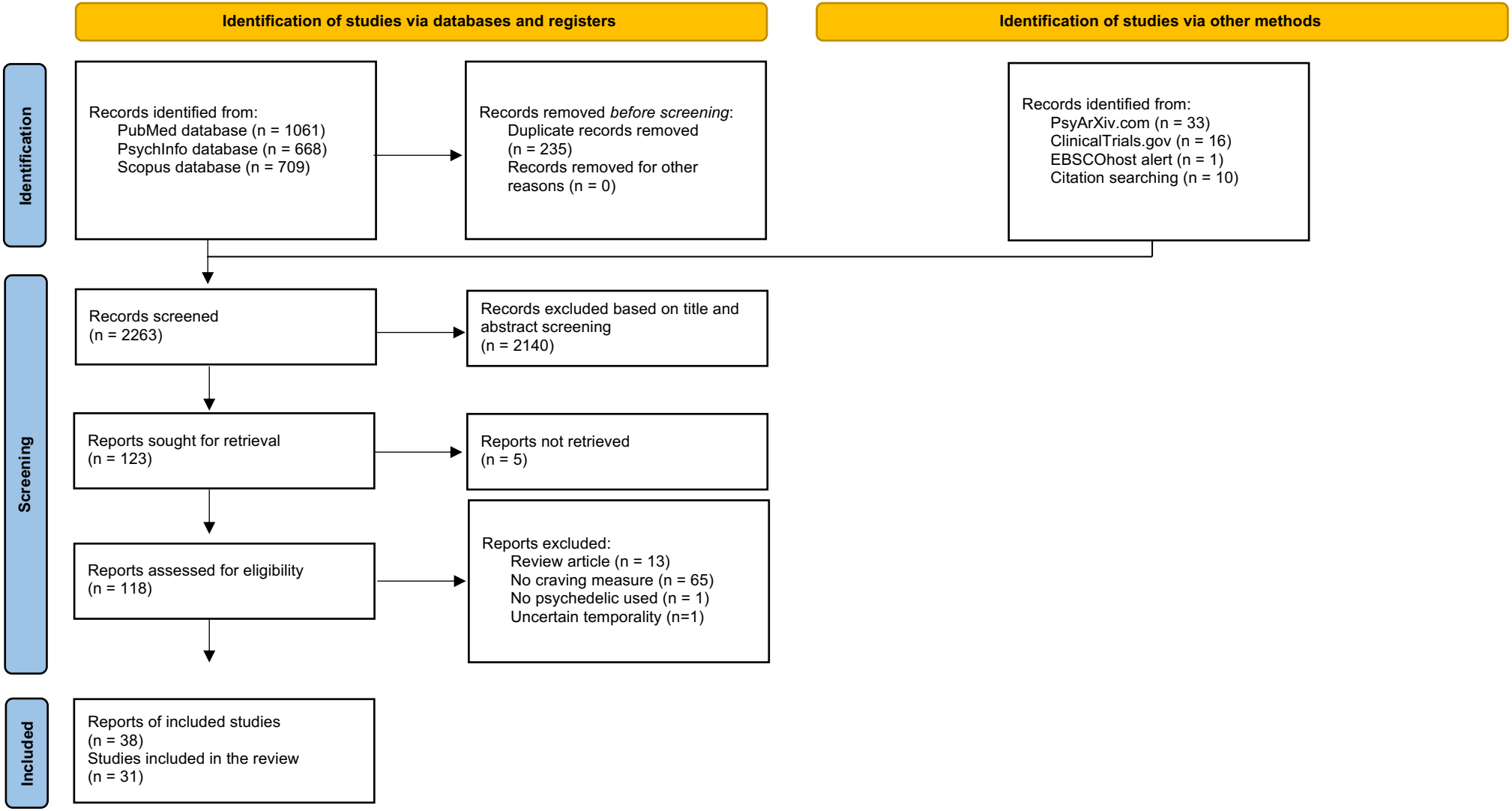
pertained to five distinct studies (Dakwar et al., 2017; Dakwar et al., 2018), (Johnson et al., 2014; Garcia-Romeu et al., 2014; Noorani et al., 2018), (Mash et al., 2018; Mash et al., 2001; Mash et al., 2000), and (Thomas et al., 2013; Argento et al., 2019a), (Mollaahmetoglu et al., 2021; Grabski et al., 2022), further on referred to as their main report (Dakwar et al., 2017; Mash et al., 2018; Johnson et al., 2014; Thomas et al., 2013; Grabski et al., 2022). A large cross-sectional study of 214,505 participants (Jones, 2022) met the inclusion criteria but was ultimately excluded. This study investigated the associations between lifetime use of classic psychedelics and past-month nicotine dependence using data from the National Survey on Drug Use and Health. It found that lifetime mescaline use was associated with reduced tobacco craving, whereas lifetime use of LSD or MDMA was associated with increased tobacco craving. However, its findings were of limited utility for drawing causal inferences, as it was not possible to establish whether psychedelic use occurred prior to the onset of nicotine craving. Additionally, the study's large sample size and markedly different methodology compared to the other included studies were likely to increase heterogeneity unnecessarily and potentially bias the overall results of the review.

Characteristics of the studies included

Included studies are described in **Table 1**, providing a summary of their characteristics, methods, and results.

The total sample size was 2,639 participants and ranged from one in two case reports (Barsuglia et al., 2018; Lalanne et al., 2016) to 444 participants in a qualitative cross-sectional study based on an online survey (Garcia-Romeu et al., 2020). Mean age of the participants was 37.3. Most studies included both genders with 29.67% women in total. Four studies only included men (Barsuglia et al., 2018; Krystal et al., 1998; Berlowitz et al., 2019; Rydzyński et al., 1968) and one study only women (Lalanne et al., 2016).

Figure 1.: PRISMA 2020 flow diagram for new systematic reviews



Modified from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table 1. Summary of the characteristics, methods, and results of the included studies, by psychedelic assessed

Table 1.a Ketamine

Study			Sample				Intervention				Outcomes	
1st author	Year	Design	N	Age (range or mean (SD))	Gender (% women)	SUD	Substance, dose, route	Number of sessions	Setting (PAP)	Control	Addiction outcome (if data available: mean (SD))	Craving assessment methods and results (if data available: mean (SD))
Krystal	1998	RCT	3 (control) vs 9 (low dose) vs 6 (high dose)	44 (10.5)	0	alcohol	ketamine 0.1 and 0.5 mg/kg IV	2 active sessions & 1 control session	Medical (no)	saline solution	not measured	**VAS: non-significant increase** in craving following high or low doses of ketamine relative to placebo (ketamine high dose: 19.5 (7.0) to 25.8 (7.8); ketamine low dose: 18.2 (6.8) to 23.2 (7.1); placebo: 15.0 (4.7) to 18.9 (5.6))
Krupitsky	2002	RCT	35 vs 35	23.0 (4.4) (high dose group) 21.6 (3.0) (low dose group)	22.9 (high dose group) 20 (low dose group)	heroin	ketamine 2.0 mg/kg IM	1 session	medical (yes)	sub-psychedelic dose of ketamine (0.20 mg/kg) IM	rate of abstinence in the high dose group significantly higher than that of the low dose group	**VAS: significantly greater decrease in the high dose group** (ketamine high dose: 29.24 (27.32) to 3.97 (5.04); ketamine low dose: 36.34 (24.88) to 15.06 (16.54); $p < .001$)
Krupitsky	2007	RCT	26 (multiple sessions) vs 27 (single session)	22.6 (3.9)	16.9	heroin	ketamine 2.0 mg/kg IM	3 sessions in 2 months	medical (yes)	only 1 session	abstinence in 50% of the participants in the multiple sessions compared to 22.2% in the single session group ($p < 0.05$)	**VAS: no significant difference** between the single and multiple sessions groups (single session: 22.8 (5.4) to 7.2 (2.9); multiple sessions: 20.1 (4.7) to 6.09 (2.6) at 1 month)

Dakwar	2014	RCT	8 (cross over trial)	47.5 (5.5)	12.5	cocaine base	ketamine 0.41 mg/kg then 0.71 mg/kg IV	2 sessions in 9 days	medical (no)	lorazepam 2 mg	URICA: increased motivation for changing cocaine use	**VAS: significant decrease** in cue-induced cocaine craving (sum VAS change scores 24h post infusion: median 65 vs. -126, p = .012)
Lalanne	2016	Case report	1	36	100	opioid	ketamine 1 mg/kg PO	daily for 3 weeks	medical (no)	none	COWS: score of 0/11 in the first and second week after reducing opioid medication	**Authors statement: "no cravings while opioid treatment was being reduced"** (3 weeks)
Dakwar	2017	RCT	20 (cross Over trial)	48.6 (6.1)	45	cocaine	ketamine 0.71 mg/kg IV	1 session	medical (no)	midazolam (0.025 mg/kg)	average cocaine self-administration choices: decrease at 28h post infusion (1.61 with ketamine vs 4.33 choices with midazolam) (P<0.0001)	**VAS: significant decrease prior to discharge** (59.6 vs 15.3%, P = 0.01) but not at subsequent time-points
Dakwar	2019	RCT	28 (midazolam) vs 27 (ketamine)	47 (9.3)	25.5	cocaine	ketamine 0.5 mg/kg IV	1 session	medical (yes)	midazolam 0.025 mg/kg	odds of end-of-study abstinence in the ketamine group was 6 times that in the midazolam group (p=0.02)	**VAS: significant decrease** (craving scores 58.1% lower in the ketamine group than the midazolam group (p=0.01))
Das	2019	RCT	30 (RET+KET) vs 30 (no RET+KET) vs 30 (RET+PBO)	27.48 (8.11)	38.9	alcohol	ketamine not reported	1 session	medical (yes)	saline solution	general alcohol consumption from baseline to post manipulation: decrease with ketamine associated with retrieval/destabilization procedure of alcohol- maladaptive reward memories (p<0.001)	**ACQ: significant reductions with ketamine associated with retrieval/destabilization procedure** (p < 0.001) with no significant reduction in the control groups including ketamine alone
Dakwar	2020	RCT	23 (midazolam) vs	53 (9.8)	52.5	alcohol	ketamine 0.71 mg/kg IV	one	medical (yes)	midazolam (0.025 mg/kg)	likelihood of abstinence 21 days post-infusion: significant quadratic	**VAS: no significant difference**

			17 (ketamine)								effect of time (p=0.004)	
Azhari	2020	open label	8	42.5 (13.5)	50	cannabis	ketamine 0.71 mg/kg IV	1 or 2 session(s)	medical (yes)	none	Significant decrease in days of use per week (baseline: 5.1, SE = 0.7; at 6 weeks: 0.5, SE = 0.3)	**VAS: no significant difference** (baseline: 30.5 (35.47); 24h post infusion: 14.38 (22.9); week 4: 7.38 (11.4); week 6: 22.13 (20.23))
Grabski	2022	RCT	48 (control) vs 48 (ketamine)	44.07 (10.59)	36.5	alcohol	ketamine 0.8 mg/kg IV	3 sessions	medical (yes)	Saline solution	greater percentage of days abstinent at 6-month (mean difference: 10.1 (1.1, 19.0)	**ACQ: no significant difference** (ketamine vs placebo: -0.4 (-0.7; 0.0)

Table 1.b Various classic psychedelics

Study			Sample				Intervention				Outcomes	
1st author	Year	Design	N	Age (range or mean (SD))	Gender (% women)	SUD	Substances, dose, route	Number of sessions	Setting (PAP)	Control	Addiction outcome (if data available: mean (SD))	Craving assessment methods and results (if data available: mean (SD))
Rydzyński	1968	open-label	14	25 to 55	0	alcohol	LSD 100 to 800 µg, psilocybin 9 mg IM	6 to 30 sessions, rotation between substances	medical (yes)	none	statement: moderate to complete improvement in 12/14 participants	**Authors statement:** "usually, after the first two shocks and before the leading doctor starts active psychotherapy, (the alcoholic) **loses his desire for drinking**"
Johnson	2017	observational cross-sectional (qualitative)	358	31.1 (11.2)	14.5	tobacco	ayahuasca, DMT, LSD, mescaline, morning glory seeds, psilocybin	not reported	various	none	38.3% of the participants reported complete smoking cessation after the psychedelic experience, 27.9% a persisting reduction and 33.8% a	**QSU: decrease** from 111.6 (26.1) prior to the psychedelic-occasioned smoking cessation or reduction to 87.5

											temporary reduction before returning to baseline smoking	(37.3) in the present tense
Garcia-Romeu	2019	observational cross-sectional (qualitative)	343	31.4 (10.8)	22	alcohol	ayahuasca, DMT, LSD, mescaline, psilocybin	one experience	various	none	AUDIT-C before/after the psychedelic experience score change of -5.8 (3.0); drinks per week: decrease from 25.5 (21.5) before to 4.3 (10.2) after the reference psychedelic experience	**AUQ: significant decrease** from 38.8 (10.0) before to 13.4 (6.8) after the reference psychedelic experience ($p < 0.0001$)
Garcia-Romeu	2020	observational cross-sectional (qualitative)	444	28.4 (10.6)	20.9	cannabis opioid stimulant	DMT, LSD, mescaline, psilocybin	one experience	various	none	DUDIT-C before/after the psychedelic experience score change of −5.4 (3.2); range: 4 to −12. SUD diagnosis before/after: 95.7% to 27.3%	**DUQ: decrease** from 40.7 (10.4) before to 16.1 (8.9) after the reference psychedelic experience

Table 1.b Psilocybin

Study			Sample				Intervention				Outcomes	
1st author	Year	Design	N	Age (range or mean (SD))	Gender (% women)	SUD	Substance, dose, route	Number of sessions	Setting (PAP)	Control	Addiction outcome (if data available: mean (SD))	Craving assessment methods and results (if data available: mean (SD))
Johnson	2014	open-label	15	51 (10.5)	33.3	tobacco	psilocybin 20 mg/70kg then 30/70kg	2 to 3 sessions in 15 weeks	medical (yes)	none	significant reductions in self-reported daily smoking from intake to 6-month follow-up	**QSU: significant decrease** across 10 time points from intake to 6-month follow-up ($p<.001$)
Bogenschutz	2015	open-label	10	40.1 (10.3)	40	alcohol	psilocybin 0.3 then 0.4 mg/kg PO	2 sessions in 12 weeks	medical (yes)	none	percent heavy drinking days from baseline to weeks 5–12: mean difference of 26.0 (22.4) ($p = 0.008$)	**PACS: significant decrease** (baseline: 16.00 (5.59); week 8: 11.56 (5.85); week 9: 10.00 (6.61); week 12: 12.11 (8.28); week 36: 8.11 (9.16))

Table 1.c Ayahuasca

Study			Sample				Intervention				Outcomes	
1st author	Year	Design	N	Age (range or mean (SD))	Gender (% women)	SUD	Substance, dose, route	Number of sessions	Setting (PAP)	Control	Addiction outcome (if data available: mean (SD))	Craving assessment methods and results (if data available: mean (SD))
Thomas	2013	observational cross-sectional	12	38	45.5	alcohol, cocaine, painkillers tobacco	ayahuasca 50–100 mL PO	2 sessions in 4 days	ritual	none	4WSUS at 6 months: trend to a decrease for all substances except cannabis, with statistically significant decrease for cocaine	**Interviews: 8 in 12 participants reported complete cessation of cravings**
Loizaga-Velder	2014		14	42	not reported	alcohol, cocaine, cocaine base	ayahuasca	not reported	ritual	none	interviews: "All of the ritual participants reported that participation in ayahuasca rituals had been pivotal for achieving and sustaining abstinence or less harmful patterns of drug use."	**Interviews: 9 in 14 participants reported a decrease in cravings**
Talin	2017	observational cross-sectional (qualitative)	7	not reported	not reported	Alcohol, cocaine, cocaine base, heroin, methadone, tobacco	ayahuasca	not reported	ritual	none	not reported	**Interviews: craving loss in 2 of 7 participants**: "it simply cancelled the craving. […] The Daime completely erases the desire of the body and the mind"
Cruz	2018	observational cross-sectional (qualitative)	40	35	5	cocaine base	ayahuasca	not reported	ritual	none	statement: "Ayahuasca tea consumed within a religious context helped the study participants quit crack"	**Interviews: decrease in craving mentioned by 2 participants:** "The desire for the drug disappeared and was replaced by other feelings, such as guilt,

												thankfulness, and repentance."
Daldegan-Bueno	2022	observational cross-sectional	441	34.19 (10.9)	52.8	tobacco	ayahuasca	1 session (n=139), >1 session (n=231), not sure (n=71)	ritual	none	Online survey: 69.2% reported quitting after the experience, 18.3% reported reducing and 12.5% reported quitting then relapse	**QSU-Brief: Significant group** ($W(1) = 24.605$, $p < 0.0001$), **time** ($W(1) = 1480.247$, $p < 0.0001$) **and interaction effect** ($W(1) = 112.629$, $p < 0.0001$)
Berlowitz	2019	cohort	53	30.86 (8.17)	0	substances	ayahuasca	Multiple sessions	ritual	none	ASI: significant differences for drug ($d= 1.59$, $p < .001$) and alcohol ($d= 1.21$, $p < .001$) use scores	**CEQ-F: significant decrease in overall substance craving** from baseline to treatment completion ($r= .60$, $p < .001$)

Table 1.d Ibogaine

Study			Sample				Intervention				Outcomes	
1st author	Year	Design	N	Age (range or mean (SD))	Gender (% women)	SUD	Substance, dose, route	Number of sessions	Setting (PAP)	Control	Addiction outcome (if data available: mean (SD))	Craving assessment methods and results (if data available: mean (SD))
Heink	2017	observational cross-sectional (qualitative)	27	35.11 (7.85)	44	alcohol or substances	ibogaine	not reported	various	none	not reported	**Self-questionnaire: "92% of the participants reported that ibogaine "reduced" or "dramatically reduced" drug cravings** in the first four weeks after treatment"
Brown	2018	cohort	30	29.0 (9.0)	16.7	opioid	ibogaine 1,540 to 2,460 mg	1 session	medical (no)	none	ASIC Drug Use score: decrease from baseline (0.40 (0.08)) to 1 (0.11 (0.09)), 3, 6, 9 and 12 months (0.17 (0.10))	**Interviews: decrease in craving mentioned by 1 participant**: "you could safely say that iboga will give an

												opiate addict several months to a half a year of freedom from cravings and an expanded awareness."
Malcolm	2018	observational cross-sectional	50	31.28 (8.38)	39	opioid	ibogaine 18 to 20 mg/kg PO	1 session	medical (yes)	none	COWS: significant differences between pre- and post-ibogaine scores ($p < 0.01$)	**BSCS: significant differences** between pre- and post-ibogaine scores ($p < 0.01$)
Mash	2018	open-label	191	35.8 (9.9) (opioids) 36.1 (9.1) (cocaine)	33 (opioids) 15 (cocaine)	cocaine, opioid	ibogaine 8–12 mg/kg PO	1 session	medical (yes)	none	Statement: "withdrawal signs and symptoms at post dose assessments markedly reduced compared to pre-dose baseline withdrawal severity measures"	**HCQ-29 and CCQ-45: significant decrease for all subscores**; (factor 2/purposefulness: cocaine: baseline: 4.10 (0.23); discharge: 2.21 (0.15); 1 month: 2.04 (0.22) ($p=0.0001$); heroin: baseline: 2.60 (0.14); discharge: 1.54 (0.20); 1 month: 1.57 (0.09) ($p=0.0001$))
Barber	2020	observational cross-sectional (qualitative)	101	not reported	not reported	substances	ibogaine	not reported	various	none	not reported	**Forum threads: decrease in craving** and reward response to substances
Rodríguez-Cano	2022	observational cross-sectional (qualitative)	13	37 (7.7)	31	substances	ibogaine	not reported	various	none	not reported	**Interviews: cravings were eliminated in 11 out of 13 respondents and resurfaced** days or weeks after the experience

Table 1.e Mixed or various classic and atypical psychedelics

Study			Sample				Intervention				Outcomes	
1st author	Year	Design	N	Age (range or mean (SD))	Gender (% women)	SUD	Substances, dose, route	Number of sessions	Setting (PAP)	Control	Addiction outcome (if data available: mean (SD))	Craving assessment methods and results (if data available: mean (SD))
Barsuglia	2018	case report	1	31	0	alcohol	DMT, ibogaine 17.9mg/kg (I), 5 to 7mg (D, inhaled)	1 session each in 4 days	medical (yes)	none	abstinence at 1 month, decrease from 6 (baseline) to 2 drinks per week at 3 months	**Interviews: "(the patient) reported feeling no cravings for alcohol."** (at 110 h post ibogaine) "At 1-month follow-up (…) the patient reported (…) experiencing minimal cravings."

Table 1.f MDMA

Study				Sample					Intervention					Outcomes	
1st author	Year	Design		N	Age (range or mean (SD))	Gender (% women)	SUD		Substance, dose, route	Number of sessions	Setting (PAP)	Control		Addiction outcome (if data available: mean (SD))	Craving assessment methods and results (if data available: mean (SD))
Sessa	2021	open-label		14	48	42.9	alcohol		MDMA 187.5 mg PO	2 sessions in 8 weeks	medical (yes)	none		units of alcohol per week: decrease from 130.6 in the month before detoxification to 18.7 units after nine months	**PACS: decrease in percentage of participants with PACS scores>20** (cut off) (baseline: 28.6%; 3 months: 7.7%; 6 month: 0%; 9 months: 14.3%)

Abbreviations: ACQ: Alcohol Craving Questionnaire; ASI: Addiction Severity Index; ASIC: Addiction Severity Index, Composite score; AUDIT-C: Alcohol Use Disorders Identification Test – Consumption; AUQ: Alcohol Urge Questionnaire; BSCS: Brief Substance Craving Scale; CCQ: Cocaine craving Questionnaire; CEQ-F: Craving Experience Questionnaire, Frequency form; COWS: Clinical Opioid Withdrawal Symptoms; DUDIT-C: Drug Use Disorder Identification Test-Consumption; DUQ: Drug Urge Questionnaire; HCQ: Heroin Craving Questionnaire; IM: Intramuscular; IV: Intravenous; KET: ketamine; MDMA: 3,4-methylenedioxymethamphetamine; NDSS: Nicotine Dependence Syndrome Scale; No RET: retrieval/destabilization of control (non-drinking) memories; PACS: Penn Alcohol Craving Scale; PAP: Psychedelic-Assisted Psychotherapy; PBO: placebo; PO: Per Os; QSU: Questionnaire on Smoking Urges; RCT: Randomized Controlled Trial; RET: retrieval/destabilization of maladaptive alcohol memories; SD: Standard Deviation; SE: Standard Error; SUD: Substance Use disorder; URICA: University of Rhode Island Change Assessment; VAS: Visual Analog Scale; 4WSUS: 4 Week Substance Use Scale.

Synthesis of results

Craving assessment methods:

Craving was part of the secondary outcomes in most included studies. Craving assessment methods were heterogeneous, including single-item visual analog scales (Krystal et al., 1998; Krupitsky et al., 2002; Krupitsky et al., 2007; Dakwar et al., 2014; Dakwar et al., 2017; Dakwar et al., 2019; Dakwar et al., 2020; Azhari et al., 2021); SUD-specific craving questionnaires such as QSU (Johnson et al., 2014; Johnson et al., 2017; Daldegan-Bueno et al., 2022), ACQ (Das et al., 2019; Grabski et al., 2022), PACS (Sessa et al., 2021; Bogenschutz et al., 2015), AUQ (Garcia-Romeu et al., 2019), DUQ (Garcia-Romeu et al., 2020), BSCS (Malcolm et al., 2018), CEQ (Berlowitz et al., 2019), and HCQ-NOW and CCQ- NOW (Mash et al., 2018); and a study-specific questionnaire (Heink et al., 2017). The qualitative results were obtained through semi-structured interviews (Thomas et al., 2013; Loizaga-Velder and Verres, 2014; Talin and Sanabria, 2017; Barsuglia et al., 2018; Brown and Alper, 2018; Cruz and Nappo, 2018; Rodríguez-Cano et al., 2023) or forum threads (Barber et al., 2020). Two studies (Lalanne et al., 2016; Rydzyński et al., 1968) did not specify the craving assessment method used.

Changes in craving levels following psychedelic use

Twelve out of the 31 included studies reported a significant decrease in craving scores following psychedelic administration, including five randomized controlled trials using ketamine in the treatment of cocaine (Dakwar et al., 2017; Dakwar et al., 2014; Dakwar et al., 2019), opioid (Krupitsky et al., 2002) or alcohol use disorders (Das et al., 2019), two open-label trials using psilocybin in the treatment of tobacco (Johnson et al., 2014) and alcohol use disorders (Bogenschutz et al., 2015), two studies using ibogaine in the treatment of opioid (Malcolm et al., 2018) and opioid and cocaine (Mash et al., 2018) use disorders, two studies using ayahuasca in the treatment of tobacco (Daldegan-Bueno et al., 2022), and substance use

disorders (Berlowitz et al., 2019), and one online survey evaluating the impact of various psychedelics on alcohol use disorder (Garcia-Romeu et al., 2019).

Seven studies reported a decrease in craving scores after psychedelic use but did not perform inferential statistics. These studies included one randomized controlled trial using ketamine in the treatment of opioid use disorder (Krupitsky et al., 2007), two open-label trials using MDMA (Sessa et al., 2021) and LSD and psilocybin (Rydzyński et al., 1968) in the treatment of alcohol use disorder, one case report on the use of ketamine in the treatment of opioid use disorder (Lalanne et al., 2016), and three online surveys evaluating the impact of ibogaine on alcohol or substance use disorders (Heink et al., 2017), and of various psychedelics on tobacco (Johnson et al., 2017) or cannabis, opioid and stimulant use disorders (Garcia-Romeu et al., 2020).

In eight qualitative studies, participants reported a decrease in craving following the use of ayahuasca in the context of cocaine (Cruz and Nappo, 2018; Loizaga-Velder and Verres, 2014; Talin and Sanabria, 2017; Thomas et al., 2013), alcohol (Loizaga-Velder and Verres, 2014; Thomas et al., 2013; Talin and Sanabria, 2017), tobacco (Talin and Sanabria, 2017; Thomas et al., 2013), opioid (Talin and Sanabria, 2017), and painkillers (Thomas et al., 2013) use disorders; following the use of ibogaine in the context of opioid (Brown and Alper, 2018) and substance (Rodríguez-Cano et al., 2023; Barber et al., 2020) use disorders, and following the use of ibogaine and 5-MeO-DMT for the treatment of alcohol use disorder (case report) (Barsuglia et al., 2018).

Three randomized controlled trials found no significant difference in alcohol craving (Krystal et al., 1998; Dakwar et al., 2020; Grabski et al., 2022), and one open label trial found no significant difference in cannabis craving (Azhari et al., 2021) following ketamine infusions.

Craving level change over time

Craving level changes over time among studies reporting available quantitative data is displayed in **Figure 2**. Among the 12 studies reporting a decrease in craving level after psychedelic administration, 6 studies reported a statistically significant sustained decrease in craving score at one (Dakwar et al., 2019; Mash et al., 2018), six (Johnson et al., 2014), nine months (Bogenschutz et al., 2015; Das et al., 2019), and two years (Krupitsky et al., 2002) follow-up.

Conversely, one study reported a decrease in craving at 24h but not at subsequent time-points after ketamine infusion in the treatment of cocaine use disorder (Dakwar et al., 2017), one study reported a further increase of craving days or weeks after the psychedelic use for the majority of the respondents (Rodríguez-Cano et al., 2023), while another study stated the need of some participants for additional "booster doses" of ibogaine to alleviate craving for longer term (Barber et al., 2020).

Meta-analysis

Given the high level of clinical diversity and methodological heterogeneity among the included controlled trials, we were not able to perform a meta-analysis of their results on craving measures. Indeed, among the nine double-blind, placebo-controlled trials using ketamine as intervention (Dakwar et al., 2017; Dakwar et al., 2014; Dakwar et al., 2020; Dakwar et al., 2019; Grabski et al., 2022; Krupitsky et al., 2002; Das et al., 2019; Krupitsky et al., 2007; Krystal et al., 1998), only five displayed sufficient information allowing meta-analysis (Grabski et al., 2022; Krupitsky et al., 2002; Das et al., 2019; Krupitsky et al., 2007; Krystal et al., 1998). These trials used heterogeneous interventions, comparators, study designs, and time point of craving measure (Table 1), with the exception of only two studies, evaluating the impact of ketamine on ACQ scores with a parallel group study design (Grabski et al., 2022; Das et al., 2019).

Risk of bias

Risk of bias assessment scores are presented in **Table 2**. Among the studies assessed using the Risk of Bias (RoB-2) tool, two studies had a "low" overall bias score (Grabski et al., 2022; Dakwar et al., 2020), whereas five and two studies were respectively assessed as having "some concern" (Dakwar et al., 2017; Dakwar et al., 2014; Dakwar et al., 2019; Das et al., 2019; Krystal et al., 1998) and "high" (Krupitsky et al., 2002; Krupitsky et al., 2007) overall bias scores. Among the studies assessed using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I), four studies were assessed as having a "serious" (Sessa et al., 2021; Bogenschutz et al., 2015; Johnson et al., 2014; Mash et al., 2018), and two studies a "critical" (Rydzyński et al., 1968; Azhari et al., 2021) overall bias score. The studies assessed using the Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies (Thomas et al., 2013; Daldegan-Bueno et al., 2022; Johnson et al., 2017; Garcia-Romeu et al., 2020; Garcia-Romeu et al., 2019; Malcolm et al., 2018; Heink et al., 2017) were all assessed as "unsatisfactory". The studies assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies had a mean score of 3/9 (Berlowitz et al., 2019; Brown and Alper, 2018). The studies assessed using the COnsolidated criteria for REporting Qualitative research (COREQ) checklist displayed a mean total number of included items of 15.25/32 (Loizaga-Velder and Verres, 2014; Talin and Sanabria, 2017; Rodríguez-Cano et al., 2023; Barber et al., 2020). The studies assessed using the CAse REports (CARE) checklist had a mean total number of included items of 20.5/30 (Lalanne et al., 2016; Barsuglia et al., 2018).

Table 2. Risk of bias assessment of the included studies

Table 2.a revised Risk of Bias (RoB-2) tool results

RoB 2.0 results						
Studies	*Randomization process*	*Deviations from intended interventions*	*Missing outcome data*	*Measurement of the outcome*	*Selection of the reported result*	*Overall bias*
Krystal et al. 1998	Some concerns	Some concerns	Low	Low	Low	Some concerns
Krupitsky et al. 2002	Some concerns	High	High	Low	Some concerns	High
Krupitsky et al. 2007	Some concerns	Some concerns	High	Low	Low	High
Dakwar et al. 2014	Some concerns	Low	Low	Low	Low	Some concerns
Dakwar et al. 2017	Some concerns	Low	Low	Low	Low	Some concerns
Dakwar et al. 2019	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Das et al. 2019	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns
Dakwar et al. 2020	Low	Low	Low	Low	Low	Low
Grabski et al. 2022	Low	Low	Low	Low	Low	Low

Table 2.b Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool results

ROBINS-I results								
Studies	*Bias due to confounding*	*Selection of participants*	*Classification of interventions*	*Deviations from intended interventions*	*Missing data*	*Measurement of outcomes*	*Selection of the reported result*	*Overall bias*
Rydzyński et al. 1968	Critical	Low	NI	NI	NI	Critical	Low	Critical
Johnson et al. 2014	Moderate	Low	Low	Low	Low	Serious	Serious	Serious

Bogenschutz et al. 2015	Serious	Low	NI	Low	Moderate	Moderate	Low	Serious
Mash et al. 2018	Serious	Low	Low	NI	Moderate	Serious	Low	Serious
Sessa et al. 2021	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Azhari et al. 2020	Critical	Low	Critical	Low	Low	Critical	Serious	Critical

Table 2.c Newcastle-Ottawa Scale (NOS) results

NOS results adapted for cross-sectional studies									
Studies	*Selection: representativeness of the sample*	*Selection: sample size*	*Selection: non-respondents*	*Selection: ascertainment of the exposure (risk factor)*	*Comparability of subjects in different outcome groups on the basis of design or analysis.*	*Outcome: assessment of outcome*	*Outcome: statistical test*	*Total score*	*comment*
Thomas et al. 2013	0/1	0/1	0/1	0/2	0/2	1/2	1/1	2/10	Unsatisfactory Studies
Heink et al. 2017	0/1	0/1	0/1	0/2	0/2	1/2	0/1	1/10	Unsatisfactory Studies
Johnson et al. 2017	0/1	0/1	0/1	0/2	0/2	1/2	0/1	1/10	Unsatisfactory Studies
Malcolm et al. 2018	0/1	0/1	0/1	2/2	0/2	1/2	1/1	4/10	Unsatisfactory Studies
Garcia-Romeu et al. 2019	0/1	0/1	0/1	0/2	2/2	1/2	1/1	4/10	Unsatisfactory Studies

Garcia-Romeu et al. 2020	0/1	0/1	0/1	0/2	2/2	1/2	0/1		3/10	Unsatisfactory Studies
Daldegan-Bueno et al. 2022	0/1	0/1	0/1	0/2	2/2	1/2	1/1		4/10	Unsatisfactory Studies
NOS results for cohort studies										
Studies	*Selection: representativeness of the exposed cohort*	*Selection: selection of the non-exposed cohort*	*Selection: ascertainment of exposure*	*Selection: demonstration that outcome of interest was not present at start of study*	*Comparability of cohorts on the basis of the design or analysis*	*Outcome: assessment of outcome*	*Outcome: was follow-up long enough for outcomes to occur*	*Outcome: adequacy of follow up of cohorts*	*Total score*	
Brown et al. 2018	0/1	0/1	1/1	1/1	0/2	0/1	1/1	1/1	4/9	
Berlowitz et al. 2019	0/1	0/1	0/1	1/1	0/2	0/1	1/1	0/1	2/9	

Table 2.d COnsolidated criteria for REporting Qualitative research (COREQ) checklist

COREQ checklist									
Studies	*Domain 1: Research team and reflexivity: personal characteristics*	*Domain 1: Research team and reflexivity: relationship with participants*	*Domain 2 : Study design : theoretical framework*	*Domain 2: Study design: participant selection*	*Domain 2 : Study design : setting*	*Domain 2 : Study design : data collection*	*Domain 3: analysis and findings: data analysis*	*Domain 3: analysis and findings: reporting*	*Total number of included items:*
Loizaga-Velder et al. 2014	3/5 items	0/3 items	1/1 item	2/4 items	1/3 items	2/7 items	1/5 items	4/4 items	14/32
Talin et al. 2017	1/5 items	0/3 items	1/1 item	2/4 items	2/3 items	3/7 items	0/5 items	3/4 items	12/32
Barber et al. 2020	2/5 items	1/3 items	1/1 item	4/4 items	2/3 items	2/7 items	3/5 items	4/4 items	19/32
Rodríguez-Cano et al. 2022	2/5 items	1/3 items	1/1 item	3/4 items	2/3 items	1/7 items	2/5 items	4/4 items	16/32

Table 2.e CAse REports (CARE) checklist

CARE checklist													
Studies	*Title*	*Key Words*	*Abstract*	*Introduction*	*Patient Information*	*Clinical Findings*	*Timeline*	*Diagnostic Assessment*	*Therapeutic Intervention*	*Follow-up and Outcomes*	*Discussion*	*Patient Perspective*	*Informed Consent*	*Total number of included items:*
Lalanne et al. 2016	1/1 item	1/1 item	4/4 items	1/1 item	1/4 items	0/1 item	1/1 item	0/4 items	2/3 items	3/4 items	4/4 items	0/1 item	1/1 item	19/30
Barsuglia et al. 2018	1/1 item	1/1 item	3/4 items	0/1 item	3/4 items	1/1 item	1/1 item	3/4 items	2/3 items	3/4 items	4/4 items	0/1 item	0/1 item	22/30

DISCUSSION

The primary aim of this systematic review was to determine if the use of psychedelics was associated with changes in craving in humans. Among the 16 studies that reported inferential statistics, 12 reported a statistically significant decrease in craving for tobacco, alcohol, or other substances. Ketamine was used in five studies; psilocybin, ibogaine, and ayahuasca in two studies each; and various psychedelics in one study. Of these positive studies, five were randomized controlled trials, three were open-label trials, three were observational cross-sectional studies and one was an observational cohort study. All positive studies were assessed as "unsatisfactory", or having "some concerns", "high risk" or "serious" risk of bias. The decrease in craving levels lasted for one to several months following psychedelic administration in six of these studies. Conversely, three randomized controlled trials and one open label trial did not find any reduction in craving scores following ketamine infusions. Fifteen studies reported a decrease in craving scores after psychedelic use without inferential statistics. Taken together, these results suggest that certain psychedelic treatments may have the potential to reduce cravings, paving the way for further exploration of psychedelics as a possible pharmacotherapy for addiction.

Ketamine could represent a less specific treatment option for addiction, according to these results. Indeed, the four studies reporting no statistically significant difference in craving all used ketamine in participants with alcohol (Grabski et al., 2022; Dakwar et al., 2020; Krystal et al., 1998) or cannabis (Azhari et al., 2021) use disorders. Among the eight randomized controlled trials using ketamine, three reported no significant reduction in craving measures (Grabski et al., 2022; Dakwar et al., 2020; Krystal et al., 1998), although reductions in other measures of addictive behavior (e.g. use levels) were observed. It is possible that these studies were insufficiently powered to observe a specific effect on craving, although this

discrepancy highlights the fact that the magnitude of psychedelic effects in craving specifically might be smaller than those on overall addictive behaviors.

Conversely, both studies that investigated psilocybin in the treatment of tobacco (Johnson et al., 2014) and alcohol use disorders (Bogenschutz et al., 2015) demonstrated a statistically significant reduction in craving following psilocybin administration. These findings suggest that psilocybin may be a potentially effective compound for reducing craving.

Participant's age could also affect psychedelic use impact on craving. Mean age in participants from the four negative studies (Grabski et al., 2022; Dakwar et al., 2020; Krystal et al., 1998; Azhari et al., 2021) was 45.9, versus 37.3 in the twelve studies reporting significant craving reduction (Garcia-Romeu et al., 2019)(Daldegan-Bueno et al., 2022)(Berlowitz et al., 2019; Mash et al., 2018; Malcolm et al., 2018; Bogenschutz et al., 2015; Johnson et al., 2014; Dakwar et al., 2017; Dakwar et al., 2014; Dakwar et al., 2019; Das et al., 2019; Krupitsky et al., 2002). To our knowledge, no study assessed the impact of participants' mean age on psychedelic effects. Furthermore, the longer duration of the disorder in older participants rather than the participants' age could lead to differences in treatment outcomes. Our results might also be in favor of an influence of gender on craving outcomes. Indeed, gender composition across positive and negative studies varied from 34.7% of women in the four negative studies versus 29.5% in the samples of the twelve significantly positive studies. While these qualitative comparisons cannot be taken as statistical evidence for moderation or equivalence, respectively, they should encourage further research into the role of length of disorder and gender in the outcomes of psychedelics studies.

Craving for alcohol might display a lower response to ketamine treatment than craving for other substances. Three out of four randomized controlled trials assessing the efficacy of ketamine in alcohol consumption reported negative results on craving outcome (Grabski et al., 2022; Dakwar et al., 2020;

Krystal et al., 1998), with only the study of Das *et al*. (whose participants were non-treatment seeking hazardous drinkers) reporting improvement in craving measures. Speculatively, this could be attributed to the similarity in the subjective effects of ketamine and alcohol and the involvement of the NMDA receptor in the intoxication signal for both. Accordingly, ketamine treatment may reduce craving for other substances. Four other trials using ketamine having reported a significant decrease in cocaine (Dakwar et al., 2017; Dakwar et al., 2014; Dakwar et al., 2019) and heroin (Krupitsky et al., 2002) craving, with comparable methods regarding number of ketamine infusions and doses used. In two (Dakwar et al., 2020; Grabski et al., 2022) of the three negative studies in alcohol use disorder, ketamine significantly increased alcohol abstinence in the participants, even at a 6-months follow-up (Grabski et al., 2022). These results could suggest non craving-mediated mechanisms of ketamine for reducing drinking (Worrell and Gould, 2021). According to Krupitsky et al., the increased abstinence obtained following ketamine treatment in participants with heroin addiction was likely due to factors such as a proposed "afterglow" effect, characterized by elevated mood and decreased anxiety for days or months following a psychedelic experience (Majić et al., 2015; Pahnke et al., 1970), leading to "a specific shift in the participant's mind and his or her attitude to life" (Krupitsky et al., 2007). This hypothesis remains to be adequately tested, but if supported could involve an increased ability to manage craving following the psychedelic experience.

Our review did not find robust support for psychedelic-assisted psychotherapy conferring additional benefits on craving reduction above the pharmacological effects of psychedelics alone. Among the 13 studies that incorporated psychotherapy as an adjunctive intervention to psychedelic administration in a medical setting, 3 reported no significant reduction in craving (Azhari et al., 2021; Grabski et al., 2022; Dakwar et al., 2020), while 6 did (Johnson et al., 2014; Bogenschutz et al., 2015; Krupitsky et al., 2002; Dakwar et al., 2019; Mash et al., 2018; Malcolm et al., 2018). In contrast, of the 6 studies that did not include psychedelic-assisted psychotherapy in a medical setting, only 1 found no significant reduction in

craving (Krystal et al., 1998), whereas 3 reported a significant decrease (Dakwar et al., 2017; Dakwar et al., 2014; Das et al., 2019). These results should be interpreted with caution, considering that only a small proportion of studies did not use psychotherapy alongside the use of psychedelics in their methods, and direct comparative studies will be required to adequately test the additional benefits of psychedelic-assisted psychotherapy. In addition, further caution is warranted regarding the use of psychedelics outside of a psychotherapy framework due to the potential for increased adverse events, although such events were not reported at a higher rate in studies without psychotherapy compared to those that included it.

The mechanisms of action of psychedelics in the treatment of addictions, and to which extent these mechanisms are common to classic and atypical psychedelics such as ketamine, remains to be clarified. Most authors emphasized the psychotherapeutic properties of psychedelics' subjective effects, and their importance in the healing process. The study of Thomas et al., highlighted a significant improvement in mindfulness, empowerment, hopefulness, quality of life-meaning, and quality of life-outlook after two sessions of ayahuasca in ritual settings (Thomas et al., 2013). Such properties were also observed in studies using ketamine (Dakwar et al., 2014).

Several studies highlighted an association between the psychedelic subjective experience and changes in craving scores (Dakwar et al., 2017; Johnson et al., 2014; Loizaga-Velder and Verres, 2014; Bogenschutz et al., 2015). Likewise, Bogenschutz et al. reported large correlations between measures of acute effect intensity, as measured with the Hallucinogenic Rating Scale (HRS) and the Mystical Experience Questionnaire, and change in craving following psilocybin administration in the treatment of alcohol dependence (Bogenschutz et al., 2015). Similarly, Johnson et al. found a significant correlation between mean States of Consciousness Questionnaire (SOCQ) scores and Questionnaire on Smoking Urges (QSU) scores following psilocybin administration in the treatment of tobacco use disorder, concluding to the prediction of decrease in craving by mystical experience (Johnson et al., 2014). This correlation was

also supported by the study of Dakwar et al., which reported a mediation of cocaine craving, as well as decrease in cocaine self-administration and naturalistic use, by Hood Mysticism Scale (HMS) scores, assessing acute mystical-type effects of ketamine use (Dakwar et al., 2017). It is unclear, however, to what extent the specific experiences tapped by these questionnaires are responsible for observed outcome differences, or whether their correlations simply represent greater overall sensitivity to drug effects or intensity of experience due to individual metabolic factors. Indeed, relatively mild spiritual/mystical experiences have been associated with MDMA use (and only in 10-15% of users (Sessa, 2018)), yet MDMA may have some therapeutic efficacy for SUDs. Sessa *et al*. proposed that the milder subjective experiences on MDMA may enable a better-tolerated enhancement of psychotherapy for patients with alcohol use disorder (Sessa et al., 2021). Furthermore, it has been proposed that peak mystical experiences induced by psychedelics could be of interest to produce maximal efficacy, albeit not necessary to induce therapeutic response (Olson, 2020).

Increased insight may also have contributed to the reported outcomes. Several studies included in this review highlighted increased insight following ayahuasca (Cruz and Nappo, 2018; Loizaga-Velder and Verres, 2014) and ibogaine (Heink et al., 2017; Mash et al., 2018). Many participants described vivid visions during the acute phase of the experience, often compared to waking dreams (Loizaga-Velder and Verres, 2014; Heink et al., 2017; Mash et al., 2018; Cruz and Nappo, 2018), which are frequently believed to increase participants' insight and thus increase the chance for prolonged abstinence (Donnelly, 2011). Online survey respondents also rated psychedelic experiences preceding reduction in alcohol (Garcia-Romeu et al., 2019) or other substance (Garcia-Romeu et al., 2020) use among the 10 most psychologically insightful experiences of their lives for 74% and 71% of the sample, respectively. For the latter, Drug Use Disorders Identification Test Consumption (DUDIT-C) scores were significantly associated with ratings of the experience as personally meaningful (Garcia-Romeu et al., 2020). Insight improvement could contribute

to craving decrease, as Bogenschutz et al. proposed in their Model of Possible Change Mechanisms in Hallucinogen-Assisted Treatment of addictions (Bogenschutz and Pommy, 2012).

The above-mentioned psychedelic-induced subjective experiences, also called "peak-psychedelic" experiences often pertain to mystical experiences and have been described as "experiences high in unity/oneness internally and with one's surroundings, insightfulness, knowledge of ultimate reality, and spiritual or religious sacredness" (Bogenschutz et al., 2018). These experiences have been shown to have substantial personal meaning and a spiritual significance in healthy volunteers, leading to sustained positive changes in attitudes and behavior (Griffiths et al., 2006). The link between psychedelic experience, insight gain, and craving decrease requires further investigation, but may provide a more unified psychological framework to explain the efficacy of psychedelics in the treatment of addictive disorders, although likely not to be the only mechanism of action of these compounds.

Although the monitoring of adverse events was not the primary objective of this review, we observed that such events were common but typically mild, except in one study conducted in a ritual setting where severe adverse events were reported (Loizaga-Velder and Verres, 2014). Therefore, albeit moderate, the risk pertaining to psychedelic use requires careful screening and monitoring in controlled settings (Griffiths et al., 2006; Nichols, 2016).

This systematic review presents several limitations that must be acknowledged. Craving is a complex phenomenon that varies greatly both over time and between individuals. The included studies used heterogenous and typically self-reported measures of craving. While psychometric validation has been performed on most of the questionnaire measures used to evaluate craving in this review, it is unclear how reliable verbal self-report or single-item VAS measures are. These factors contribute to disparities in apparent craving and use within individuals and to heterogeneous results between studies. Importantly,

none of the included studies had craving as their primary outcome, and the majority did not use inferential statistics. Furthermore, the intentionally broad scope of the inclusion criteria resulted in a high level of clinical diversity and methodological heterogeneity among the included controlled trials, which did not allow for the conduct of a meta-analysis of the results.

Perhaps most importantly, the overall quality of evidence of studies in the review was low. Most studies were assessed as presenting methodological concerns, such as small sample size or lack of control condition, leading to high risk of bias scores, thus encouraging caution in consideration of the results. Highlighting these issues should encourages more rigorously designed and reported future research.

Overall, our results indicate that there is some, albeit inconsistent, evidence suggesting that psychedelic substances may reduce cravings in individuals with substance use disorders, particularly 'classic' psychedelics. Whilst our review suggests craving may be involved in the efficacy of some psychedelics in the treatment of addictive disorders, the mediating impact and upstream mechanism of this action remains to be clarified. It appears possible that psychedelic use promotes several changes that lead to craving reduction and addiction improvement. These findings call for the development of studies of psychedelic interventions in addictions, to clarify through larger scale, high quality, randomized controlled trials the current results, and to better characterize the factors affecting craving changes.

In conclusion, this systematic review of the literature suggests a potentially lasting decrease in craving following the use of some psychedelics, across various settings, and substance use disorders. The subjective psychedelic experience has been proposed as a potential mechanism of action of this effect, although this remains to be adequately tested. These results should be taken with caution, given the high level of methodological diversity, the low proportion of studies using inferential statistics and the overall high risk of bias of most of the included studies. This must encourage further larger-scale trials to be conducted, to

clarify the efficacy and to better explore the mechanism of action of psychedelic substances in the treatment of addiction.

Acknowledgements: the authors wish to thank Laura Lambert and Jean-Marc Alexandre, SANPSY laboratory, CNRS UMR 6033, University of Bordeaux, Bordeaux, France, for their methodological consulting and sharing of expertise in data collection and psychometry. The authors wish to thank Steve O'Brien, Imperial College London, Centre for Neuropsychopharmacology, Division of Brain Sciences, Faculty of Medicine, London, UK, for sharing of expertise on psychedelics therapy.

Declaration of Conflicting Interests: the Authors declare that there is no conflict of interest related to this work.

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Figure caption **Figure 2**

This figure contains six plots displaying craving changes among included studies with available quantitative data. Line plots show craving questionnaires outcomes measured before psychedelic administration (Baseline), after psychedelic administration (Post Session: no detailed information regarding time of measure) and at different time points. The vertical Y-axis shows outcomes on (a) Visual Analog Scale (VAS), (b) Alcohol (ACQ), Cocaine (CCQ) and Heroin (HCQ) Craving Questionnaires, (c) Alcohol (AUQ) and Drug (DUQ) Urge Questionnaires, (d) Penn Alcohol Craving Scale (PACS), (e) Craving Experience Questionnaire (CEQ), (f) Questionnaire on Smoking Urges (QSU); the horizontal X-axis shows measurement time points. The psychedelic substance assessed is indicated by the line type, and the substance use disorder (SUD) by the color.