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REVIEW

Effects of psychedelics on opioid use disorder: a scoping review of preclinical studies

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Abstract

The current opioid crisis has had an unprecedented public health impact. Approved medications for opioid use disorder (OUD) exist, yet their limitations indicate a need for innovative treatments. Limited preliminary clinical studies suggest specific psychedelics might aid OUD treatment, though most clinical evidence remains observational, with few controlled trials. This review aims to bridge the gap between preclinical findings and potential clinical applications, following PRISMA-ScR guidelines. Searches included MEDLINE, Embase, Scopus, and Web of Science, focusing on preclinical in vivo studies involving opioids and psychedelics in animals, excluding pain studies and those lacking control groups. Forty studies met criteria, covering both classic and non-classic psychedelics. Most studies showed that 18-methoxycoronaridine (18-MC), ibogaine, noribogaine, and ketamine could reduce opioid self-administration, alleviate withdrawal symptoms, and change conditioned place preference. However, seven studies (two on 2,5-dimethoxy-4-methylamphetamine (DOM), three on ibogaine, one on 18-MC, and one on ketamine) showed no improvement over controls. A methodological quality assessment rated most of the studies as having unclear quality. Interestingly, most preclinical studies are limited to *iboga* derivatives, which were effective, but these agents may have higher cardiovascular risk than other psychedelics under-explored to date. This review strengthens support for translational studies testing psychedelics as potential innovative targets for OUD. It also suggests clinical studies need to include a broader range of agents beyond *iboga* derivatives but can also explore several ongoing questions in the field, such as the mechanism of action behind the potential therapeutic effect, safety profiles, doses, and frequency of administrations needed.

Keywords Psychedelics · Opioid use disorder · Dependence · Withdrawal · Self-administration · Conditioned place preference

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Introduction

Opioid use disorder (OUD), a public health problem of increasing concern, has emerged as one of the most prevalent causes of overdose-related deaths among adults aged 25 to 64 [1, 2]. Although we count on approved medications for the treatment of OUD, they have some limitations. These include the presence of residual withdrawal symptoms, high dropout rates from treatment, and high relapse rates [3, 4]. Concerning the more prevalent use of high-potency synthetic opioids like fentanyl, opioid overdose-associated mortality increased from 68,630 individuals in 2020 to 80,411 in 2021 (CDC WONDER online database) [5]. In response to the ongoing opioid crisis, the National Institutes of Health (NIH) is collaboratively launching a comprehensive initiative targeting three scientific domains. The initiative aims to enhance overdose-reversal and prevention interventions, discover innovative medications for OUD treatment, and identify safe, nonaddictive interventions for chronic pain management [6]. Thus, due to the burgeoning morbidity and mortality rates associated with OUD, the interest in and necessity of investigating alternative therapies has become more salient [6, 7].

Psychedelic compounds have been studied as treatments for various substance use disorders (SUDs) [8–11]. These compounds are classified based on their different mechanisms of action and chemical structures. One group is the "Classic" psychedelics, which includes mescaline, lysergic acid diethylamide (LSD), psilocybin, N, N-dimethyltryptamine (DMT, in *ayahuasca*), 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT), and 4-acetoxy-dimethyltryptamine (4-AcO-DMT). These compounds act as agonists of the serotonin (5-HT) 2 A receptors (5HT2A). In contrast, "non-classic" psychedelics exert their effects by interacting with different neurotransmitter receptor systems. This category includes iboga alkaloids, which are compounds derived from the *Tabernanthe iboga* plant: ibogaine, its derivative (noribogaine), and its synthetic analog (18-Methoxycoronaridine (18-MC)) [12]. Other compounds in this group are ketamine and 3,4-methylenedioxymethamphetamine (MDMA) [11, 13].

Classic psychedelics can be further classified by their chemical structures into tryptamines (psilocybin, psilocin, DMT, and 5-MeO-DMT), ergolines (LSD and D-lysergic acid amide), and phenethylamines (2,5-Dimethoxy-4-iodoamphetamine (DOI), 2,5-Dimethoxy-4-methylamphetamine (DOM), mescaline, 4-Bromo-2,5-dimethoxyphenethylamine (2 C-B), and 4-Iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine (25I-NBOMe)) [14]. Both classic (LSD, 5-MeO-DMT, ayahuasca, mescaline, psilocybin) and non-classic substances (ibogaine, ketamine, MDMA), have been explored for the treatment of various SUDs with promising results [11, 13]. Classic psychedelics interact with serotonin receptors, potentially impacting mood regulation and cognitive processes [15]. Non-classic psychedelics, with heterogeneous mechanisms including dopamine antagonism and N-methyl-D-aspartate (NMDA) agonism, may reduce dopamine levels in animal studies, impacting addiction's reward systems [1, 8, 16–18]. They also interact with the opioid system and serotonin receptors, suggesting potential therapeutic roles in substance use disorders [16]. Detailed descriptions of the specific pharmacology of each psychedelic compound are beyond the scope of this review.

The number of controlled clinical trials on psychedelics for OUD is limited, as revealed in our review of clinical trials (PROSPERO protocol CRD42023392307) [19]. Given recent literature highlighting challenges in the design of clinical trials for OUD (i.e., ethical concerns around having a placebo arm, challenges in blinding treatment groups, etc.) [20], the emphasis on preclinical data becomes particularly relevant. The absence of a viable placebo treatment analog for psychedelics presents a significant hurdle for future clinical trials [21]. Additionally, draft FDA guidance regarding the design of psychedelic trials has raised concerns about the lack of explicit reports of addiction to psychedelics in existing studies, although recommendations for assessing potential addiction of Schedule I compounds are outlined in FDA draft guidance [22].

There are previous reviews exploring the preclinical literature on the use of psychedelics in the treatment of other substance use disorders [23–25]. However, the available literature is limited as it pertains to OUD. For instance, only one previous narrative review examined preclinical evidence on ibogaine/noribogaine [26]. In the current manuscript, we aim to review a broader range of psychedelics. This is the first preclinical scoping review specific to OUD, incorporating classic (DMT, DOI, and DOM) and non-classic psychedelics (ibogaine, noribogaine, ketamine, and 18-MC). We examine the effects of psychedelics across several outcomes with translational potential, such as withdrawal, self-administration, and conditioned place preference (CPP) in animals with opioid dependence. In addition, we systematically assess the methodological quality of all the manuscripts reviewed.

Methods

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) guidelines [27, 28]. A protocol was developed and pre-published, outlining the planned search strategy, eligibility criteria, process for screening and

Table 1 Characteristics of the studies included

Study	Animals		Sample size		Opioid		Psychedelic		Results
Author, year	Age (weeks)	Animal (Sex)	Case	Control	Dose (Administration route)	Schedule	Dose (Administration route)	Schedule	Findings
18-MC									
Glick, 1996.2	12	Rats (F)	~6/group	~6/group	Morphine (0.04 mg/kg/infusion) (i.v.)	~6 weeks	10, 20, 30, or 40 mg/kg (i.p.)	Multiple doses	All doses significantly decreased morphine SA; 3 doses of 40 mg/kg 18-MC generated prolonged aftereffects (for at least two weeks), while 1 or 2 doses did not
Glick, 2002	NR	Rats (F)	6–8	6–8	Morphine (0.04 mg/kg/infusion) (i.c.)	Two weeks	1–2 mg/kg (i.p.)	Single dose	No difference in comparison with control group
Glick, 2006	NR	Rats (F)	5–10	5–10	Morphine (0.1 mg/kg/infusion) (i.v.)	Two weeks	1–20 µg (i.c.)	Single dose	Decreased morphine SA when administered locally on the medial habenula or the interpeduncular area. No effect when administered on the ventral tegmental area
King, 2000	NR	Rats (F)	5–11 per group (3 testing groups)	5–11	Morphine (0.04 mg/kg/infusion) (i.v.)	NR	NR (p.o.)	Single dose	Significant effect of treatments on morphine SA. There was no significant difference between (-), (+) and (-+) enantiomers
Maisonneuve, 1999	NR	Rats (F)	6	6	Morphine (5 mg/kg) (i.p.)	Two weeks	40 mg/kg (i.p.)	Single dose	18-MC selectively interfered with morphine-induced dopamine release, without altering morphine-induced stimulation of dopamine synthesis
Maisonneuve, 2003	NR	Rats (F)	~10 (5 for 18-MC and 5 for Ibogaine)	5	Morphine (0.04 mg/kg) (i.v.)	~Two weeks	40 mg/kg, ascending doses (both) (i.p. and i.c.)	Single dose	Dose-response reduction in the SA with 18-MC treatment (10 mg/kg minimum effective dose for morphine) Interpeduncular-administered 18-MC significantly reduced morphine SA
Panchal, 2005	NR	Rats (F)	5–8	5–8	Morphine (20–80 mg/kg) (s.c.)	Seven days	5 µg, 10–20 µg (i.c.)	Single dose	18-MC into the locus coeruleus, interpeduncular nucleus, and medial habenula significantly reduced some withdrawal signs; Some doses of 18-MC administered into the interpeduncular nucleus exacerbated diarrhea and teeth chattering
Rho, 1998	NR	Rats (F)	6–8/group	8	Morphine (10 and 20 mg/kg on the 1st day, 40 and 60 mg/kg on the 2nd day, and 60 and 80 mg/kg on the 3rd and subsequent days) (s.c.)	Seven days	10, 20, or 40 mg/kg (i.p.)	Single dose	18-MC was shown to attenuate signs of morphine withdrawal in rats
4-AcO-DMT									
Vargas-Perez, 2017	NR	Rats and mice (M)	8	8	Heroin (0.5 mg/kg) (s.c.) Morphine (10 mg/kg) (i.p.)	Five days	4 mg/kg for rats; 10 mg/kg for mice (i.p.)	Single dose	The conditioned place aversion associated with opiate withdrawal was blocked in 4-AcO-DMT pretreated rodents
DOI									
Martin, 2021	8	Rats (M)	5–6	5–6	Fentanyl (2.5 µg/kg/injection) (i.v.)	Five days	0.0-0.4 mg/kg (i.p.)	Multiple doses	The same economic demand parameters that increase following fentanyl experience are decreased by acute activation of the 5-HT2A receptor by DOI
DOM									

Table 1 (continued)

Study	Animals		Sample size		Opioid		Psychedelic		Results
Author, year	Age (weeks)	Animal (Sex)	Case	Control	Dose (Administration route)	Schedule	Dose (Administration route)	Schedule	Findings
Maguire, 2013	Adult	Monkeys (M/F)	4	4	Heroin (0.0001-0.1 mg/kg/infusion) (i.v.)	NR	0.1 and 0.32 mg/kg (i.v.)	Multiple doses	DOM alone did not maintain responding that was significantly different from responding maintained by saline
Maguire, 2023	Adult	Monkeys (M/F)	6	6	Fentanyl (0.1, 0.32, 1.0, and 3.2 mg/kg/infusion) (i.v.)	NR	0.032, 0.1, and 0.32 mg/kg (i.v. and s.c.)	Multiple doses	DOM did not significantly alter fentanyl choice
Ibogaine									
Cappendijk, 1994.1	NR	Rats (M)	20	10	Morphine (75 mg) (s.c.)	NR	40 mg/kg (i.p.)	Single dose	Ibogaine: Induced tremor and excitatory behavior; Attenuated some withdrawal signs Norharman: Decreased locomotion; Attenuated some withdrawal signs
Cappendijk, 1994.2	Adult	Rats (M)	10	10	Morphine (75 mg) (s.c.)	Pellet implanted for 72 h	40 mg/kg (i.p.)	Single doses	Attenuated the opioid withdrawal syndrome and favored the inhibitory role of the drug in the expression of morphine abstinence
Dworkin, 1995	Adult	Rats (M)	5	5	Heroin (0.17 µg/infusion) (i.v.)	NR	40 and 80 mg/kg (i.p.)	Multiple doses	Reduction in the SA. Both doses completely suppressed the use of heroin for one day
Dzoljic, 1988	Adult	Rats (M)	10/group	10	Morphine (85 mg) (s.c.)	Pellet implanted for 72 h	4, 8, and 16 µg (i.c.)	Single dose	A dose-related reduction in some parameters of withdrawal. The animals presented decreased locomotor activity
Frances, 1992	NR	Mice (NR)	20	20	Morphine (50–100 mg/kg) (i.p.)	Five days	30 mg/kg (i.p.)	Single dose	Ibogaine did not reduce withdrawal symptoms
Glick, 1991	12	Rats (F)	4–12	4–12	Morphine (0.01 mg/infusion) (i.v.)	Two weeks	2.5–80 mg/kg (i.p.)	Multiple doses	A dose-related decrease in morphine SA, especially in doses of 10 mg/kg or higher
Glick, 1992	12	Rats (M)	27	17	Morphine (NR) (s.c.)	34 days	20, 40 or 80 mg/kg (i.p.)	Single dose	Ibogaine significantly decreased some withdrawal effects
Glick, 1994	12	Rats (F)	3–8	3–8	Morphine (NR) (i.v.)	Two weeks	20–40 mg/kg (i.p.)	Multiple doses	All the iboga alkaloids produced acute reductions in morphine SA for at least a day afterwards. R-ibogamine produced the most consistent aftereffects
Glick, 1997	12	Rats (F)	6	6	Morphine (0.04 mg/kg/infusion) (i.v.)	~Two weeks	40 mg/kg (i.p.)	Single dose	Ibogaine alone reduced the SA of morphine. When it was administered in combination with norBNI and NMDA, this effect was inhibited
Glick, 1998	~12	Rats (F)	NR	NR	Morphine (0.04 mg/kg/infusion) (i.v.)	Seven days	40 mg/kg (i.p.)	Single dose	Reduction in morphine SA
Leal, 2003	Adult	Mice (M)	12–15	12–15	Morphine (25-50 mg/kg) (i.p.)	Three days	40–80 mg/kg (i.p.)	Single dose	Ibogaine reduced withdrawal signs at 64% with 40 mg/kg and 97% with 80 mg/kg
Luxton, 1996	NR	Rats (M)	8/group	8	Morphine (5 mg/kg) (i.p.)	2–3 days	40–80 mg/kg (i.p.)	Single dose	A single injection of ibogaine did not interfere with the expression of a morphine-induced CPP

Table 1 (continued)

Study	Animals		Sample size		Opioid		Psychedelic		Results
Author, year	Age (weeks)	Animal (Sex)	Case	Control	Dose (Administration route)	Schedule	Dose (Administration route)	Schedule	Findings
Parker, 1995	NR	Rats (M)	7–10	7–10	Morphine (5 mg/kg) (i.p.)	Four weeks	40 mg/kg (i.p.)	Multiple doses	Ibogaine prevented the establishment of a one-trial morphine-induced CPP, but this effect was not maintained after four training trials. Results suggest that ibogaine may only modulate a weak preference or repeated exposure to ibogaine reduces its efficacy in attenuating the rewarding effect of morphine
Parker, 2002	NR	Rats (M)	30	30	Morphine (20 mg/kg) (s.c.)	Two doses	40 mg/kg (i.p.)	Single dose	Ibogaine decreased withdrawal-precipitated place aversion, and also decreased some withdrawal signs compared to control groups
Sharpe, 1990	NR	Rats (M)	24	24	Morphine (75 mg) (s.c.)	Three days	5, 10, 20 or 40 mg/kg (s.c.)	Single dose	Ibogaine was not effective in reducing withdrawal in animal model
Ketamine									
Asl, 2004	NR	Mice (M)	9/group	9	Morphine (50 mg/kg) (s.c.)	Four days	25, 50, and 75 mg/kg (i.p.)	Multiple doses	Some withdrawal signs were decreased for all dosages, and others were decreased for the 50 mg/kg and 75 mg/kg groups
Brent, 1993	Adult	Guinea-pig (M/F)	5	5	Morphine (15 mg/kg) (s.c.)	Single dose	20 mg/kg (s.c.)	Single dose	Dose-related sedation and flaccidity, abolished the locomotor activity and behavior during morphine withdrawal
Gao, 2003	NR	Mice (M)	8–10	8–10	Morphine (10 mg/kg) (s.c.)	Five days	10 mg/kg (i.p.)	Multiple doses	Ketamine significantly inhibited morphine CPP
Gonzalez, 1997	12–15	Mice (M)	10	10	Morphine (300 mg/kg) (s.c.)	Single dose	2, 4, and 8 mg/kg (s.c.)	Single dose	Ketamine attenuated morphine tolerance and physical dependence with all doses
Ji, 2004	Adult	Rats (M)	47*	47	Morphine (5–50 mg/kg) (i.p.)	Five days	Group 1: 2, 4, 8 and 16 mg/kg; Group 2: 2–16 mg/kg; Group 3: 4–100 µg; Group 4: 0.4–10 µg (i.p.)	Multiple doses	Some withdrawal signs were dose-dependently suppressed by repeated i.p. ketamine (8 and 16 mg/ kg) or i.c. ketamine (100 µg)
Koyuncuoğlu, 1991	NR	Rats (M)	11–12	10	Morphine (5 mg/kg) (i.p.)	Five days	40 mg/kg (i.p.)	Multiple doses	More intense abstinence syndrome was manifested by the rats previously given ketamine or dextromethorphan than by those not given ketamine or dextromethorphan previously
McKendrick, 2020	5–8	Mice (M)	17	23	Morphine (10 mg/kg) (i.p.)	Five days	10 mg/kg (R, S)-ketamine (i.p.)	Single dose	Ketamine reduced morphine CPP
Streel, 2001	Adult	Rats (M)	10	10	Morphine (day 1 = 20, 20, 30; day 2 = 40, 40, 50; day 3 = 50 and 100) (s.c.)	Three days	10 mg/kg (i.m.)	Single dose	Ketamine reduced the global withdrawal score
Suzuki, 2000	NR	Mice (M)	8	8	Morphine (5 mg/kg) (s.c.)	Six days	1, 3 or 10 mg/kg (i.p.)	Single dose	Ketamine suppressed morphine CPP

Table 1 (continued)

Study	Animals		Sample size		Opioid		Psychedelic		Results
Author, year	Age (weeks)	Animal (Sex)	Case	Control	Dose (Administration route)	Schedule	Dose (Administration route)	Schedule	Findings
Witkin, 2020	NR	Rats and mice (M)	8 rats; 8–13 mice	8 rats; 8–13 mice	Morphine (5 mg/kg i.p. or 10 mg/kg s.c.)	12 days	10 or 20 mg/kg (R)-ketamine (s.c.)	Single dose	(R)-ketamine significantly attenuated the morphine-induced CPP
Zhai, 2008	NR	Rats (M)	10	9	Morphine (5 mg/kg) (s.c.)	Eight days	60 mg/kg (i.p.)	Single dose	Suppression of morphine CPP
Noribogaine									
Glick, 1996.1	12	Rats (F)	5–6	5–6	Morphine (0.04 mg/kg) (i.v.)	Two weeks	40 mg/kg (i.p.)	Single dose	For the first day, the intake of morphine decreased. Morphine response persisted for the second day, increased progressively through the days until resume to the baseline on the 7th day intake
Mash, 2016	Adult	Mice and rats (M)	27	11	Morphine (25-75 mg/kg) (s.c.)	Three days	10–100 mg/kg (p.o.)	Single dose	Some withdrawal signs were reduced up to 89% compared to the vehicle-treated mice with the maximum dose of 100 mg/kg. At the same time, noribogaine did not demonstrate any statistical change in CPP scores up to test doses of 100 mg/kg

Legend 18-MC, 18-methoxycoronaridine; 4-AcO-DMT, 4-Acetoxy-N, N-dimethyltryptamine; 5-HT2A, 5-hydroxytryptamine (serotonine) 2 A receptors; CPP, conditioned place preference; DOI, 2,5-dimethoxy-4-iodoamphetamine; DOM, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane; F, female; i.c., intracerebral; i.m., intramuscular; i.p., intraperitoneal; i.v., intravenous; M, male; NR, not reported; norBNI, nor-binaltorphimine; p.o., per os (by mouth); SA, self-administration; s.c., subcutaneous. Note: * 6 (single i.p. injection of ketamine), 9 (repeated i.p. injection of ketamine), 9 (i.c. microinjection of ketamine), 13 (ketamine microinjection into NAc), 10 (ketamine microinjection into amygdala)

selecting studies, and data extraction. The protocol was registered on the Open Science Framework [29].

Information sources and search strategy

The following databases were searched to identify relevant literature: Ovid MEDLINE, Embase (Ovid), Web of Science (WoS), and Scopus. A medical subject heading (MeSH) analysis of known key articles provided by the research team was done, and scoping searches were performed in each database with the assistance of a medical librarian (MCF). An iterative process was used to translate and refine the searches. The formal search used controlled vocabulary terms and synonymous free-text words to maximize sensitivity. A search filter was used to identify animal studies [30]. The search strategy was peer-reviewed by a second librarian, not otherwise associated with the project, using the PRESS standard [31]. A draft MEDLINE search strategy is included in the supplementary material (Supplementary Table S2). Reviewers checked included studies for additional relevant citations and citing articles. Search results were pooled in EndNote (www.endnote.com) and deduplicated using the Yale Reference Deduplicator (library.medicine.yale.edu/reference-deduplicator). This set was uploaded to Covidence (www.covidence.org) for screening.

Eligibility criteria

Only preclinical in vivo studies examining the impact of psychedelics on opioid use outcomes in animals within an opioid dependence model were included. The present review excluded non-hallucinogenic psychedelics other than 18-MC. This decision was based on their inability to induce altered perception, which aligns with the definition of a psychedelic [32]. However, 18-MC was included as an exception due to its growing clinical applications and the significant number of studies retrieved for this substance during pilot searches conducted prior to the formal start of the present review. There were no restrictions on animal type, language, region, or year of publication. Only papers that examined a control group were included, with or without blinding. The exclusion criteria were concomitant use of other substances, studies such as those investigating pain-related opioid use or cancer pain, case reports, and case series.

Selection of sources of evidence and data charting

For study selection, two or more reviewers (APS, HNPO, TPP, RK, CF) participated in the screening of papers. An additional reviewer was consulted for studies where the reviewers disagreed (GAA). The data was extracted to

Table 1, with the following information: authors, year of publication, sample size, opioid use regimen, psychedelic type, psychedelic use regimen, and main findings.

Methodological quality assessment

Three authors (APS, HNPO and TPP) independently assessed the methodological quality of the included studies using the SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) tool [33]. The tool consists of ten domains that analyze possible bias. The domains are sequence generation, baseline characteristics, allocation concealment, random housing, performance blinding, random outcome assessment, detection blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain was analyzed individually and plotted on a graph. We did not provide an overall methodological quality for the studies, as the tool does not recommend methods to judge studies in this fashion.

Results

Forty studies investigating psychedelics' impact on opioid use outcomes were included in the final analysis (Fig. 1), encompassing the following psychedelics: ibogaine, noribogaine, 18-MC, ketamine, DOM, 4-AcO-DMT, and DOI.No eligible studies were found for some searched substances (e.g., DMT, psilocybin, ayahuasca, and mescaline). An evidence atlas was produced (Fig. 2) to display the countries where the included studies were carried out using the MapChart [34].

Methodological quality assessment

The result of the methodological quality assessment can be found in Fig. 3. All the studies were considered to have an unclear explanation of the sequence generation domain, as none mentioned how the animals were placed in their boxes/cages. Likewise, the random housing domain was unclear because of the lack of explanations regarding box placement in the rooms. All the studies were also unclear for the other

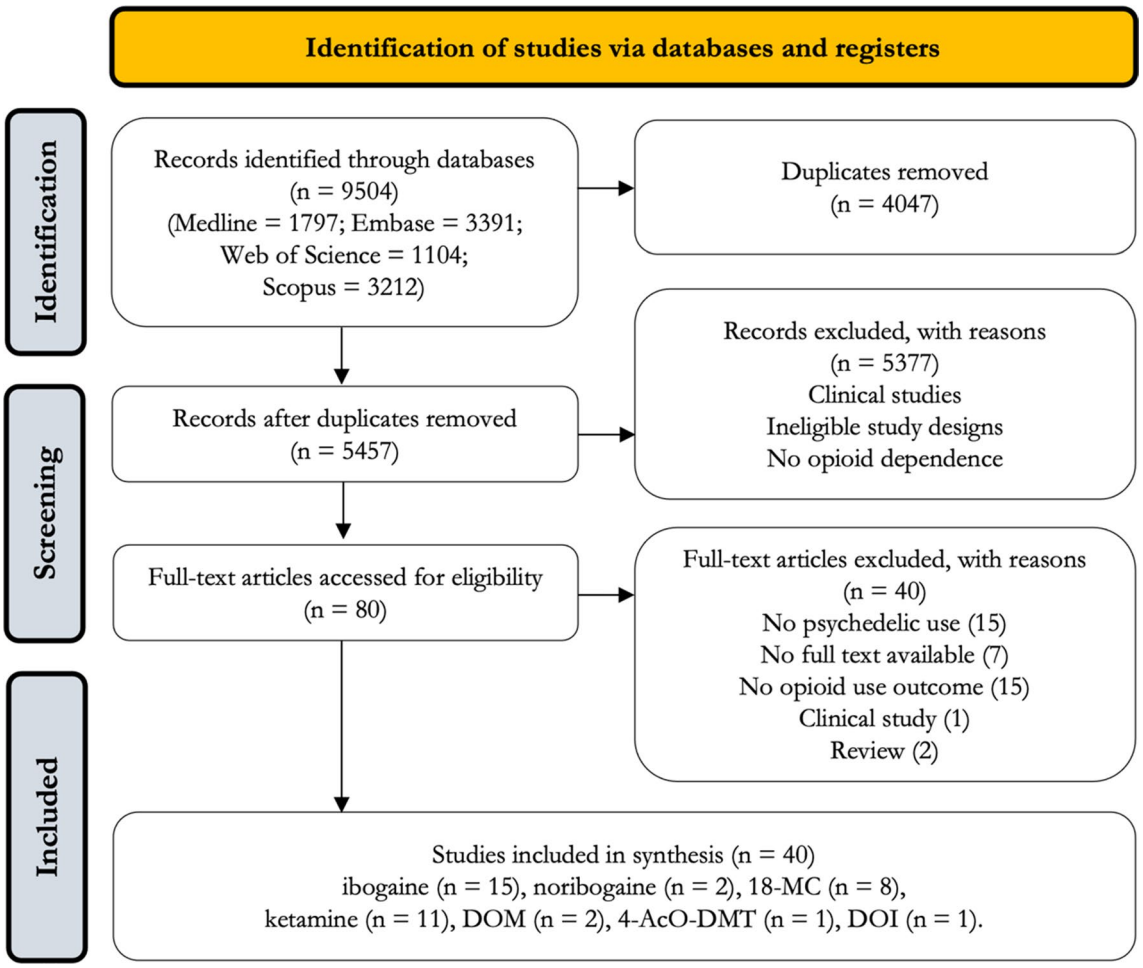

Fig. 1 Flow diagram showing inclusion and exclusion strategy

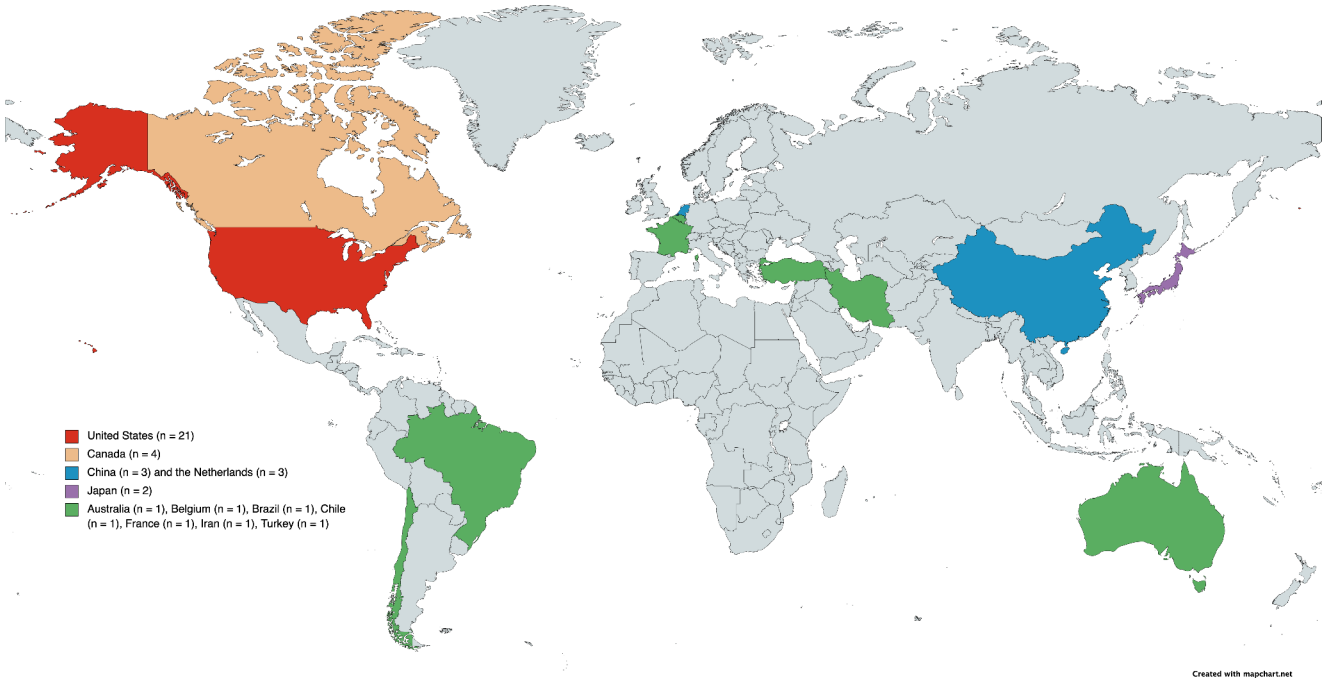

Fig. 2 Evidence atlas showing the distribution of the included preclinical trials

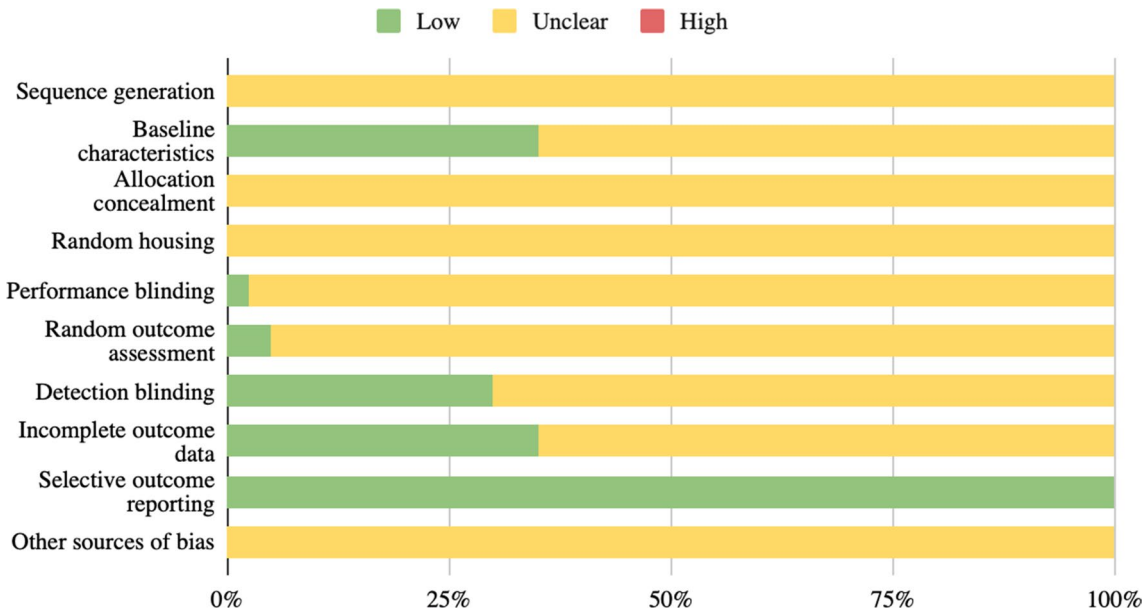

Fig. 3 Methodological quality assessment of the included studies

sources of bias, mainly due to the lack of clarity around animal replacement due to dropouts and animal caging. Another critical issue, judged unclear for all studies, was the allocation concealment, as most did not mention animal randomization to treatment/control groups. Few studies, even though mentioning randomization, did not explain how it was performed, maintaining the unclear entry. For the baseline characteristics, we only considered low-risk bias studies that specifically described at least animal type, sex, and age [9, 35–47]. The others were considered unclear due to the possible heterogeneity of animals included. Investigator blinding was performed only in one study [10], while detection blinding was performed in 12 of them [10, 38, 47–56]. As for incomplete outcome data, some studies showed inconsistencies in the number of animals analyzed, or animals initially included, sometimes not providing an exact number of animals analyzed, which we judged as unclear risk of bias [9, 10, 36–42, 44, 46, 47, 50, 51, 53, 55–65]. As

for selective outcome reporting, all studies were considered to have low risk of bias, as they all reported results for the outcomes they aimed to measure.

Psychedelics' impact on opioids

The studies included in the analysis spanned the period from 1988 to 2023. The number of studies pertaining to each respective psychedelic compound were as follows: ibogaine ($n=15$), noribogaine ($n=2$), 18-MC ($n=8$), ketamine ($n=11$), DOM ($n=2$), 4-AcO-DMT ($n=1$), and DOI ($n=1$). Study characteristics, encompassing the first author's last name, specific psychedelic utilized, dosage and administration schedule, and main findings, are detailed in Table 1. Moreover, our findings are summarized in a schematic way in Fig. 4.

Classic Psychedelics

Tryptamines

4-AcO-DMT

Conditioned place preference/aversion Place preference tests are commonly used in preclinical studies to assess the rewarding or aversive properties of substances [8, 66]. These tests involve conditioning animals to associate specific environments with the effects of a drug or treatment [65, 66]. Place preference indicates a preference for the environment associated with the drug's rewarding effects, while place aversion indicates avoidance of an environment associated with aversive effects.

A study examined the impact of 4-AcO-DMT on male Wistar rats to determine its effectiveness in blocking both the conditioned aversive response to opiate withdrawal and

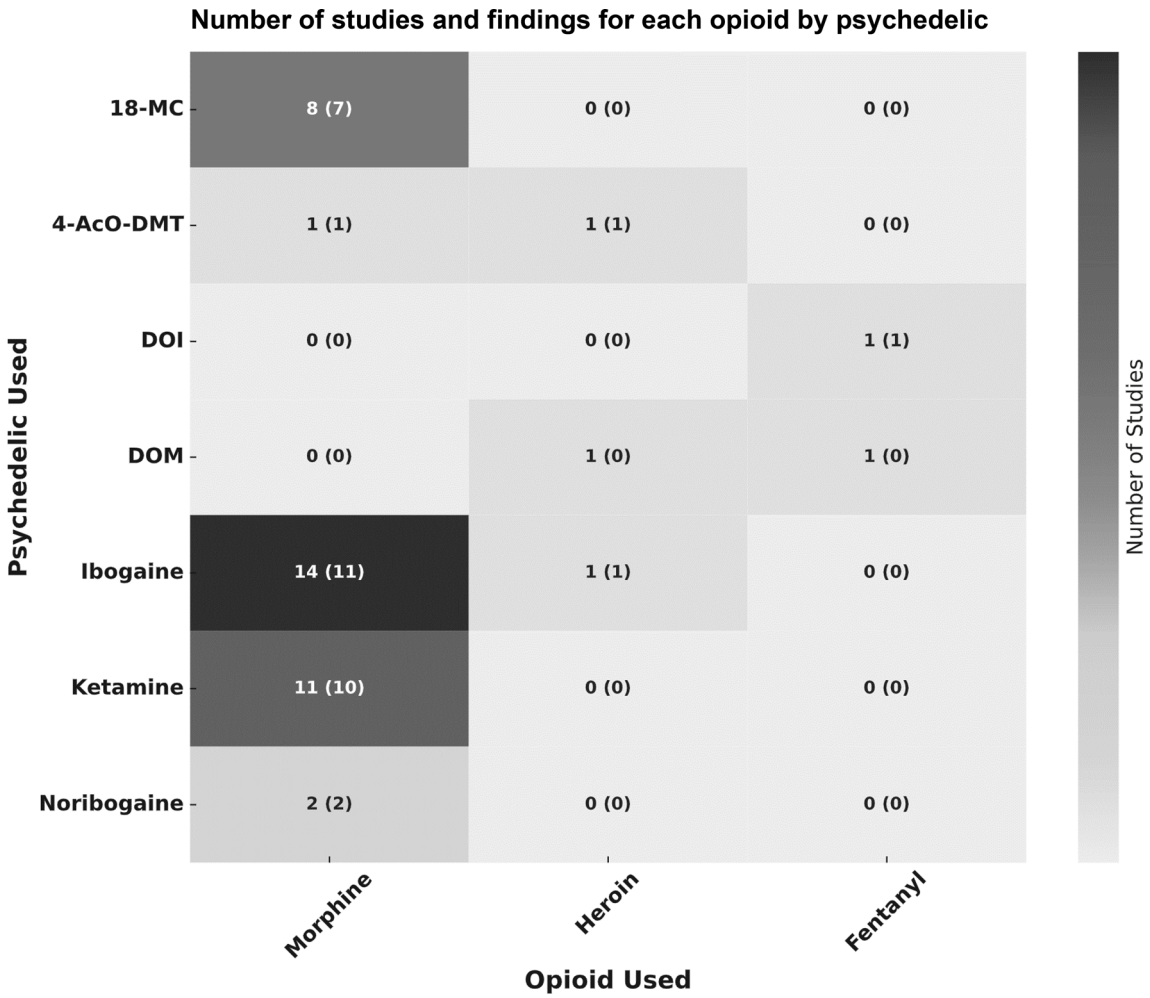

Fig. 4 Schematic summarization of the results in a heatmap. The heatmap displays the number of preclinical studies conducted for each psychedelic-opioid combination. Each cell contains two numbers: the first number represents the total number of studies, and the number in parentheses indicates the number of studies that reported positive findings with psychedelic agent in the paradigm/OUD outcome

the development of CPP [65]. Researchers induced opioid dependence by administering heroin (0.5 mg/kg, subcutaneously) to the rats over a five-day period. Prior to conditioning sessions, the rats received a single dose of 4-AcO-DMT (4 mg/kg, intraperitoneal) or a vehicle. In the first experiment, researchers aimed to assess whether 4-AcO-DMT could block the development of preference for the environment paired with morphine. The conditioning involved morphine administration (3 mg/kg, intraperitoneal) in one environment and no treatment in another, over 4–8 days with sessions lasting 40 min each. Results indicated that 4-AcO-DMT, administered before morphine exposure, prevented CPP for the motivational effects of morphine, compared to the control group. The second experiment focused on the motivational aspects of naloxone-precipitated and spontaneous opioid withdrawal. The study setup was similar to the first experiment, with the main difference being the testing of 4-AcO-DMT's capacity to decrease the aversion for the environment paired with naloxone induced withdrawal or the environment paired with spontaneous withdrawal. In this case, 4-AcO-DMT did not prevent the development of conditioned place aversions due to naloxone but did have an effect on spontaneous withdrawal [65]. The data from these experiments demonstrate the potential of 4-AcO-DMT in modulating the rewarding and aversive effects associated with opioid administration or opioid withdrawal, respectively.

Phenethylamines

DOI

Self-administration/opioid use The preclinical self-administration model evaluates how animals voluntarily administer drugs by performing specific actions, like pressing a lever, to receive drug doses [18, 37]. This method helps with the understanding of the addictive properties of substances and test potential treatments for addiction, by measuring factors like dose-response and drug-seeking behavior [45].

Only one in vivo study examined DOI's effect on the reduction of opioid self-administration. A group of 8-weeks-old male Sprague-Dawley rats was exposed to multiple sessions of intravenous (IV) fentanyl self-administration. After the completion of the training phase, the rats entered the testing phase, in which they received ascending intraperitoneal doses of DOI (0.1, 0.2, and 0.4 mg/kg) on different days, at least two days apart, 30 min before subsequent fentanyl self-administration sessions. The results demonstrated that the overall consumption of fentanyl decreased approximately 1.5 times after the 0.4 mg/kg administration of DOI [45].

DOM

Self-administration/opioid use Two papers evaluated the use of DOM, a 5-HT2A agonist, on opioid self-administration in rhesus monkeys. The research aimed to explore the influence of DOM on the abuse liability of opioids. In the first study, varying doses of DOM (0.1–0.32 mg/kg) were administered intravenously to monkeys before sessions involving heroin administration. The results indicated that DOM did not alter heroin self-administration behaviors in these animals [67]. The subsequent study expanded the range of DOM doses tested (0.032, 0.1, and 0.32 mg/kg) and switched the opioid to fentanyl. Similar to the heroin study, DOM did not decrease fentanyl self-administration. Additionally, when given a choice between food and fentanyl, the presence of DOM did not shift preference towards food [18]. These preclinical findings suggest that DOM, despite its interaction with the 5-HT2A receptors, does not reduce opioid self-administration in non-human primates, indicating that it may not be effective as a treatment for opioid dependence in humans based on these models.

Non-classic psychedelics

Ibogaine

Self-administration/opioid use In the preclinical trials evaluating ibogaine's impact on opioid self-administration, the doses administered ranged from 2.5 to 80 mg/kg, mostly given intraperitoneally [9, 37, 41, 53, 57]. The five studies found that the number of self-administered infusions per hour was effectively reduced [9, 37, 41, 53, 57]. The studies evaluated self-administration after using ibogaine in Sprague-Dawley, Long-Evans, and Fisher 344 rats [9, 37, 41, 53, 57].

One study with Sprague-Dawley rats demonstrated that ibogaine administration led to a dose-dependent reduction in morphine self-administration, with robust effects observed at doses greater than 10 mg/kg. Interestingly, these effects were specific to opioid self-administration and were not observed in water self-administration sessions [37]. In another study, various iboga alkaloids were tested in rats, all of which showed a dose-related decrease in morphine self-administration. The compounds exhibited important results, with duration of the reduced self-administration effect being variable among subjects from days to weeks, but whole body tremor not lasting for more than 4 h, contradicting the theory that motor inhibition alone accounted for the reduction in drug self-administration [9]. Additionally, co-administration of ibogaine with a kappa opioid receptor antagonist

(nor-binaltorphimine, norBNI) and/or a NMDA agonist (N-methyl-D-aspartic acid, NMDA) resulted in a significant inhibition of the ibogaine-induced reduction in morphine self-administration, suggesting a modulatory effect of these receptors [41]. Further investigations compared different iboga alkaloids in Sprague-Dawley and Long-Evans rats, revealing reductions in morphine self-administration for up to two days after ibogaine administration [42]. Finally, in Fisher 344 rats, both 40 and 80 mg/kg doses of ibogaine completely suppressed heroin self-administration for at least one day, with the higher dose showing prolonged effects in some cases [57]. These preclinical findings suggest that ibogaine and its derivatives hold promise as potential agents decreasing opioid self-administration.

Withdrawal In preclinical withdrawal models, animals are exposed to a drug for a period of time to induce dependence, then the drug is removed abruptly to simulate withdrawal, or in other studies withdrawal may be triggered by administering drugs such as naloxone [10, 38, 48, 49, 63]. Ibogaine has been explored for its potential to alleviate withdrawal symptoms, employing various administration routes. Motor activity, often examined as a withdrawal sign, generally shows improvement [38]. While most studies report positive effects on withdrawal signs [38, 48, 49, 63], there are exceptions [10]. For instance, in Sprague-Dawley rats, ibogaine administration led to a dose-dependent reduction in specific withdrawal manifestations, such as rearing, digging, and teeth chattering [36]. Another study noted reductions in teeth chattering, penile licking, and diarrhea [48, 49]. Additionally, ibogaine administration in mice showed inhibition of naloxone-induced jumping [63]. However, not all studies found substantial benefits; some reported minimal impact on symptoms like grooming and paw shaking [54]. Overall, ibogaine has demonstrated effectiveness in alleviating various withdrawal signs. Nonetheless, it paradoxically increased naloxone-induced jumping in one study, suggesting it may not mitigate all opioid withdrawal symptoms effectively [10].

Conditioned place preference/aversion Three studies investigated the effects of ibogaine on place preference and aversion in Sprague Dawley rats, using intraperitoneal doses ranging from 40 to 80 mg/kg [8, 52, 68]. In the initial study, ibogaine pre-treatment inhibited CPP induced by a single morphine administration, but this effect diminished after repeated exposures [8]. Subsequent research by the same authors, using an opioid-dependent model, showed no significant impact of ibogaine on established morphine CPP [68]. In another experiment, ibogaine administration significantly reduced naloxone-induced place aversion. These results indicate potential for ibogaine in mitigating the early on rewarding effects of single exposure to morphine as well as the potential to mitigate aversive effects associated with opioid withdrawal [52].

Noribogaine

Self-administration/opioid use

One study examined the efficacy of noribogaine in reducing morphine self-administration. Sprague-Dawley rats were trained for self-administration of morphine (0.04 mg/kg per response) or water for approximately 2 weeks until they reached a stable dose of self-administration per day. On the test days, they were administered a single intraperitoneal dose of 40 mg/kg of noribogaine or saline. These doses were administered 15 min before the self-administration test sessions. Results indicated that ibogaine significantly reduced morphine self-administration in the first two days, with a subsequent increase over the next five days until returning to baseline infusion levels by the seventh day [39]. The study also explored noribogaine's effect on morphine-induced locomotor stimulation. In this experiment, rats received either noribogaine or saline, and then they received a dose of morphine 19 h after (single dose of 5 mg/kg, i.p). Immediately after the morphine dose, the animals were placed in the testing cage for three hours. The results showed a significant reduction in locomotor activity during the first hour [39].

Withdrawal

One study conducted two experiments to assess the potential effects of noribogaine on naloxone-precipitated withdrawal and explored noribogaine CPP [46]. Morphine (25–75 mg/kg) was administered subcutaneously three times daily for three consecutive days, with increasing doses each day. On the fourth day, an additional dose was given before testing. Two hours after the last morphine dose, mice in the noribogaine treatment groups received intragastric doses of noribogaine. Control mice received vehicle via oral gavage. Four groups of mice were treated with varying doses of noribogaine (10, 30, 56, and 100 mg/kg), while a fifth group served as a vehicle control. Two hours after noribogaine or vehicle administration, all mice were injected with naloxone and observed four signs of precipitated opiate withdrawal for 30 min (jumping, paw tremors, body tremors and diarrhea) [46]. The results showed an inhibition in the jumping and paw tremors. The 16 mg mg/kg dose reduced by 50% both signs. The 100 mg/kg dose inhibited jumping by 75% and paw tremors by 65%. Body tremors were reduced by

50% with a 30 mg/kg dose and 80% with a 100 mg dose. The diarrhea was not significantly reduced with either of the doses. The 56 mg/kg only significantly reduced the jumping, and the 10 mg/kg dose did not significantly reduce any withdrawal sign. The most effective doses were 30 mg/kg, showing a total decrease of withdrawal signs by 74%, and 100 mg/kg, demonstrating a total reduction of 89% [46].

Conditioned place preference/aversion

Noribogaine CPP was assessed using standard three-compartment straight alleyway boxes. Animals underwent habituation sessions followed by a determination of chamber preference. Rats were then randomized into groups and received oral doses of noribogaine (10, 30, and 100 mg/kg) or vehicle, with compartments paired accordingly. Conditioning and testing occurred over multiple sessions, evaluating preference for noribogaine-paired chambers versus vehicle-paired chambers. Results showed no significant alteration in rats' preference scores, even at test doses of up to 100 mg/kg [46].

18-Methoxycoronaridine (18-MC)

Self-administration/opioid use

Six studies investigated the efficacy of 18-MC in reducing opioid self-administration, utilizing Long Evans and Sprague-Dawley rats and administering doses ranging from 1 to 40 mg/kg, with administration routes including intraperitoneal [40, 50, 59], oral [61, 64], and intracerebral [50, 60]. The studies employed similar methodologies, inducing opioid dependence through intravenous morphine self-administration for approximately two weeks before administering 18-MC. In most cases, 18-MC significantly reduced morphine self-administration compared to control. Notably, one study found that the lowest dose of 18-MC (1–2 mg/kg) was effective only when co-administered with mecamylamine (nonspecific nicotinic antagonist) [59]. Additional investigations revealed a dose-dependent reduction in morphine self-administration, with effects lasting for up to two weeks [40, 50, 61]. Furthermore, the combined administration of 18-MC with mecamylamine significantly decreased the number of infusions, highlighting the potential synergistic effects of these compounds [59]. Overall, these findings suggest that 18-MC holds promise as a potential treatment for reducing opioid self-administration in preclinical models.

Withdrawal

Two preclinical studies investigated the effects of 18-MC on withdrawal signs of morphine-dependent rats. The first study used increasing doses of morphine (20–80 mg/kg, s.c.) for seven days to generate dependence. The psychedelic treatment targeted specific brain regions, namely the medial habenula, interpeduncular nucleus, and locus coeruleus, administering varying doses of 18-MC (5 µg to 20 µg) followed by naltrexone [51]. Results indicated that, compared to the control groups, 18-MC administered into the locus coeruleus significantly reduced specific withdrawal signs, including wet-dog shakes, teeth chattering, burying, and diarrhea (4 of 7 signs). Administration into the medial habenula also significantly attenuated teeth chattering, burying, and weight loss (3 of 7 signs) compared to control groups, while interpeduncular nucleus administration significantly ameliorated rearing, teeth chattering, and burying (3 of 7 signs). Notably, some doses (10 and 20 µg) of medial habenula and interpeduncular nucleus administration exacerbated diarrhea and teeth chattering [51].

The second study, using the same morphine schedule to induce dependence, administered a single intraperitoneal dose of 18-MC (10, 20, or 40 mg/kg, intraperitoneally) to Sprague-Dawley rats, evaluating its impact on withdrawal signs precipitated by naltrexone. They found that the higher doses (20 and 40 mg/kg) of 18-MC attenuated various withdrawal signs, including diarrhea, burying, teeth chattering, wet-dog shakes, and weight loss (5 of 7 signs) [51, 53].

Ketamine

Withdrawal

Seven studies explored ketamine's effectiveness in reducing opioid withdrawal symptoms using doses from 2 to 50 mg/kg, administered intraperitoneally and subcutaneously to various animal species such as Swiss Webster mice, Wistar rats, and Sprague-Dawley rats [35, 43, 44, 56, 62, 69, 70]. Most studies reported a decrease in withdrawal symptoms following ketamine treatment [43, 69, 70]. In a study conducted with male albino Swiss Webster mice, ketamine was tested by administering it either before or after morphine. The administration attenuated tolerance, physical dependence on morphine, and withdrawal behavior, mainly when administered before morphine [43]. Similarly, in male Wistar rats made morphine-dependent, ketamine administration significantly reduced global withdrawal compared to saline controls [70]. Additionally, ketamine alleviated naloxone-precipitated withdrawal signs in morphine-dependent rats, with dose-dependent effects observed [44, 56, 69]. Similarly, ketamine administration in guinea pigs reduced locomotor

activity and other behaviors associated with morphine withdrawal [35]. However, one study with rats receiving morphine for five days followed by ketamine administration did not demonstrate positive effects and even showed more intense naloxone-precipitated withdrawal [62]. Most of the findings suggest a potential role for ketamine in mitigating opioid withdrawal.

Conditioned place preference/aversion Five studies investigated the effects of ketamine on opioid-induced place preference/aversion, utilizing doses ranging from 10 to 60 mg/kg administered intraperitoneally [55, 56, 58, 71, 72]. These studies involved C57BL/6J mice, ddY mice (Deutschland, Denken, and Yoken), and Sprague-Dawley rats and consistently demonstrated a reduction in morphine-induced CPP. For instance, in male C57BL/6J mice exposed to morphine, ketamine administration significantly reduced morphine-induced CPP [71]. Similarly, pre-treatment with ketamine suppressed morphine CPP in male ddY mice [55]. In male Sprague-Dawley rats, a single infusion of ketamine effectively suppressed morphine CPP [72]. Moreover, in male Kunming mice receiving morphine, ketamine inhibited morphine-induced CPP but also induced a significant place preference on its own [58]. Another study with male ddY mice revealed that ketamine attenuated morphine-induced place preference regardless of the dose administered, although ketamine alone did not induce CPP when administered with a vehicle [56]. These findings collectively suggest that ketamine may interfere with the rewarding effects of opioids, offering potential therapeutic implications for opioid use disorder. However, there is a cautionary note as ketamine might exhibit addictive potential.

Discussion

This scoping review explores the utilization of psychedelics in treating opioid dependence in preclinical models, encompassing a vast literature (i.e., ranging from studies as early as 1988 to 2023), and systematically examining their impact on opioid-related outcomes and behaviors. We appraised and reviewed manuscripts reporting on distinct opioid use outcomes after the administration of different psychedelics, their mechanism of action, the routes, and doses administered, the potential for clinical translation, as well as different animal types, ages, and sexes. Among the preclinical trials, ibogaine is the most extensively studied compound, followed by ketamine. Limited evidence is available for studies assessing classic psychedelics, such as mescaline, LSD, psilocybin, DMT, or ayahuasca. The studies included in this review evaluated various behavioral models, such as self-administration, withdrawal signs, and place preference/aversion. In most cases, efficacy was demonstrated by a reduction in opioid self-administration, diminished withdrawal signs, and decreased opioid-induced CPP, achieved through the use of psychedelics. Three groups did more than one study of the same psychedelic: Glick et al., Cappendijk et al., and Parker et al. However, the positive results were corroborated by other groups. Glick et al. evaluated the 18-MC effect on opioid-self administration [39, 50, 60]; this was corroborated by King et al. [61]. Glick et al. also evaluated the effect of ibogaine on opioid-self administration [9, 37, 41, 42], and this was corroborated by Dworkin et al. [57]. Cappendijk et al. and Parker et al. evaluated the effect of ibogaine on withdrawal signs [48, 49, 66], which was corroborated by Leal et al. [63].

Mechanism of action

In this review, much of the preclinical evidence stems from studies on non-classic psychedelics, which operate through diverse mechanisms beyond agonism of the serotonin 5-HT2A receptors. These mechanisms include antagonism of dopamine and NMDA receptors, agonism of serotonin 5-HT2C receptors, and interactions with κ and μ opioid receptors, among others [1, 16]. Studies on animals have demonstrated that derivatives of the iboga plant can decrease dopamine levels in the nucleus accumbens and striatum [9, 39, 64]. These psychedelics act through various mechanisms that can directly or indirectly influence the dopaminergic system. For example, a preclinical model evidenced that the activation of NMDA glutamatergic receptors could activate dopamine neurons [73]. Ibogaine, for instance, has shown potential as an NMDA antagonist. Reflecting this, its efficacy was hindered by co-administration of an NMDA receptor agonist [42] but enhanced by co-administration of an NMDA receptor antagonist (MK-801) [63]. This may elucidate the aforementioned reduction in dopamine levels. This mechanism is also shared with ketamine and is proposed to underlie the psychomimetic effects [74, 75]. Both the glutamatergic and dopamine circuits have strong connections with reward systems implicated in addiction [76–78]. However, it remains uncertain whether the efficacy of psychedelics in treating OUD is attributable to one or several of these mechanisms. Some of these non-classic psychedelics, like ketamine, have several proposed mechanisms beyond the above [79]. Perhaps the most explored mechanisms of action are those pertaining to glutamate systems, including the increase in glutamate levels by activating AMPA receptors and the blockage of NMDA [80, 81]. It has been proposed that the elevation in glutamate levels circuitry of the corticolimbic system, which is associated with drug-seeking behavior, reward mechanisms, and chronic

pain [82]. In addiction, cellular adaptations in anterior cingulate and orbitofrontal glutamatergic projections to the nucleus accumbens result in pathophysiological plasticity in excitatory transmission. This reduces the capacity of the prefrontal cortex to respond to natural rewards and provide executive control over drug-seeking, while simultaneously increasing glutamatergic response to drug-related stimuli. These changes are particularly relevant in OUD [83, 84].

Furthermore, there are also studies on the interaction of psychedelic agents with the opioid system. A study that implemented molecular simulations (e.g. G-protein recruitment essays) found an association between the μ and κ opioid receptors and ketamine [1]. In this study, the effect of ketamine was attenuated by the administration of naltrexone, an opioid antagonist that acts on the same receptors [1]. An additional example is how, in electrophysiological preclinical models, μ opioid receptors locally interact with 5-HT2A receptors in the prefrontal cortex when psychedelic agents are administered [85]. This is in fact an effect that is believed to be responsible for the hallucinogenic properties of the psychedelics [85, 86].

On the other hand, classic psychedelics do not have as wide a mechanism of action as non-classic psychedelics but can also interact with other serotonin receptors, such as 5-HT2B and 5-HT2C [15, 87]. Moreover, certain psychedelics may also affect serotonin receptors like 5-HT1, 5-HT6, and 5-HT7 [88, 89]. These receptors are involved in various brain functions, including mood regulation and cognitive processes, which could benefit OUD treatment [88].

When considering addiction treatment, the targeting of different serotonin receptors becomes significant. For instance, activating 5-HT2C receptors could also indirectly modify dopamine activity and release [90]. By modulating dopamine levels, drugs that interact with 5-HT2C receptors could potentially help in managing addiction by reducing cravings and withdrawal symptoms [91, 92].

Finally, psychedelics not only interact with serotoninergic systems but also alter synaptic density markers [56, 93], such as PSD-95, synapsin-1, synaptophysin-1, synaptotagmin-1, and SV2A. Previous preclinical and clinical work on ketamine has demonstrated its capacity to increase synaptic markers [56, 93–95]. However, there are mixed findings regarding synaptic changes when ketamine was administered under basal conditions [93]. In preclinical models, during stressful conditions, it was found that ketamine counteracted stress-related reductions in synaptic markers [93]. Synaptogenic effects of psychedelics is of potential clinical relevance as several preclinical studies have demonstrated alterations in spine density (i.e., lower) associated with exposure to opioids [96–99]. While the demonstration of the direct effects of psychedelics on spine density in humans with OUD and their clinical implications remain to be fully elucidated, it is plausible that this effect could be another potential mechanism of action.

Routes of administration and doses

The choice of the route of administration of drugs is an essential aspect in preclinical studies, as some routes could facilitate or hinder clinical translation more than others. For instance, one of the side effects observed in some rodents with ibogaine administration is marked tremor. This side effect was not observed after intracerebroventricular administration but was present after subcutaneous administration [36]. In some studies, subcutaneous doses of ibogaine were not as effective as other routes of administration, such as intraperitoneal [54]. On the other hand, examination of the efficacy of agents such as ketamine showed that systemic administration using such as subcutaneous [35, 43] or intramuscular [35, 43, 70] routes, did reduce withdrawal signs, CPP, and opioid use.

Determining the dose for each route of administration is essential. Higher doses of ibogaine and ketamine consistently reduced morphine self-administration (e.g., with doses ranging from 2.5 to 80 mg/kg of ibogaine administered intraperitoneally) [37] and attenuated withdrawal signs (e.g., with doses ranging from 25 to 75 mg/kg of ketamine administered intraperitoneally) [69]. For example, in a study with ibogaine, a dose-related improvement in withdrawal signs was reported for intracerebral administration of doses of 4, 8, and 16 μg [36]. A similar example is ketamine study showing dose-related reduction in withdrawal signs after intraperitoneal administration [44, 69].

In addition to the dose per administration, preclinical literature emphasizes the importance of the number of administrations. For instance, administering multiple doses of ibogaine was found to be helpful in animals that did not initially reduce opioid self-administration with a single dose [37]. Similar findings were observed for ketamine, where repeated intraperitoneal ketamine displayed benefits in withdrawal signs [44].

Given the diverse routes of administration and dosing ranges used across species, access to plasma drug levels can provide valuable information. Three studies have explored this outcome. Maisonneuve et al. (2003) investigated the distribution of 18-MC in plasma following its intravenous administration, revealing that the drug exhibited a terminal half-life exceeding 100 min [50]. The authors suggest that 18-MC may undergo rapid metabolism, likely with a significant first-pass effect, while its prolonged action could be due to accumulation in fat (acting as a natural storage depot). In this case, the drug stored in fat would serve as a reservoir, gradually converting to its active form over time [50]. Mash et al. (2016) reported a dose-dependent increase

in noribogaine plasma levels, with a consistent linear relationship between concentrations in both blood and brain, achieving a relative equilibrium in the brain at oral doses above 10 mg/kg [46]. Finally, Witkin et al. (2020) measured plasma levels of morphine and (R)-ketamine. The authors demonstrated that (R)-ketamine (10 and 20 mg/kg) did not significantly alter morphine plasma levels, indicating that its effects on morphine withdrawal were independent of any impact on morphine pharmacokinetics [56].

Translation to clinical practice

Our group conducted a previous review that evaluated the clinical evidence on the use of psychedelics for the treatment of opioid use disorder [19]. The clinical evidence is still scarce compared to the preclinical data. The psychedelics evaluated in our clinical review were ibogaine ($n=10$), noribogaine ($n=2$), ketamine ($n=2$), LSD ($n=1$), and ayahuasca ($n=1$). The studies revealed, in general, beneficial effects of psychedelics for the treatment of OUD. However, most clinical studies have a high risk of bias due to a lack of placebo arms and, as a result, no blinding and randomization [100].

When appraising the preclinical literature compared to the clinical one, we identified that the use of 18-MC has not been evaluated in humans. There are also significant differences in the interventions done in animals, which carry different limitations to the clinical application. For instance, the doses used per kilogram are much lower in humans vs. preclinical studies. The maximum doses used of ibogaine in humans were between 20 and 30 mg/kg [101, 102], while in preclinical studies it was 80 mg/kg [37, 38, 57]. For ketamine, the maximum dose used in humans was 2 mg/kg [103–109], while in animals, it was 75 mg/kg [69]. In clinical studies, the routes of administration were primarily oral [104–109] and intramuscular in the case of ketamine, while for preclinical studies is intraperitoneal [103, 110]. These differences in routes are important as beyond inherent differences between species, the pharmacokinetics would change between routes.

Ensuring safe and effective drug dosing is important, regardless of its intended use. There are situations in which the appropriate initial dose of a drug is yet to be defined or has not been thoroughly tested and validated for a specific species. Consequently, selecting the starting dose for research, experiments, or clinical trials in animals and humans becomes a concern [111]. Allometric scaling is a useful concept for comparing doses from preclinical studies to clinical investigations [112]. This approach involves adjusting drug doses based on body surface area to accommodate potential variations in anatomical, physiological, and biochemical factors across species [111, 113, 114]. Doses can be normalized by considering differences in pharmacokinetics and physiological time among species. For instance, for the higher doses found in the preclinical studies discussed here, the equivalent for humans would be substantially smaller [112].

Differences in opioid outcomes examined in preclinical models

Among these preclinical trials, three different methods were used to evaluate the efficacy of psychedelic treatment in opioid dependence in animals: the self-administration of opioids, mostly intravenously, the opioid-conditioned place preference/aversion, and the resolution of withdrawal symptoms, in most cases, naloxone induced. Each of these methods presents advantages and is well-known in studies of drugs with the potential for abuse. Firstly, the self-administration paradigm is considered the most direct correlation with human addictive behavior [115]. Conversely, the CPP most specifically measures the association between a stimulus and its reward, providing important insight into drug-induced craving and relapse and how these parameters change with potential treatments [47]. Lastly, studying withdrawal symptoms is an important tool to investigate better pathways that could be used as targets for treating substance use disorders [116]. Opioid withdrawal has been categorized as a state with marked hyperalgesia, increased sensitivity to pain, and hyperkatifeia, which is an increased sensitivity to negative emotional states [117]. This, added to other somatic signs and symptoms of withdrawal (e.g., changes in body temperature, insomnia, lacrimation, gastrointestinal symptoms, anhedonia) [118–121], leads to drug-seeking behavior to avoid this negative reinforcement [118, 119]. Therefore, treating these symptoms becomes essential to prevent drug-seeking.

Differences regarding animal species

The animal species chosen for conducting preclinical studies are essential in finding the one that is more proximate to the human brain. Rodents present significant genetic homology with humans [122, 123]. They are broadly used due to their cost-efficiency and short reproductive cycle, allowing multiple and faster comparisons [124]. However, their simpler brain structures are less ideal for behavioral comparisons with humans, which limits their translatability [125]. On the other hand, non-human primate brains are more structurally and functionally comparable, representing an essential model for behavioral research [126]. However, these models have been increasingly avoided due to ethical considerations [127], their longer lifespan, and more complex care requirements [128, 129]. In this review, only two

studies analyzed rhesus monkeys, investigating DOM [18, 67], in which no significant results were found compared to control groups for the studied outcomes. All the other included studies analyzed rodents of different types: Wister rats, Sprague-Dawley rats, CDF1 Mice, Fisher 344 rats, and Swiss Webster mice, while one investigated the Guinea pigs [35].

Differences between sexes

Furthermore, there is lack of exploration of the interplay between substance effects and biological sex in the context of SUD-related outcomes. Studies have indicated that males and females may exhibit distinct mechanisms of drug metabolism due to hormonal variations [130] and differing rates of drug elimination [131]. There are well-described differences in addiction between males and females. For instance, the Telescoping effect exposes the progression from the initial use of substances to the dependence phase, which is thought to be faster in women than in men for different substances, including opioids [132].

The studies included in this review did not specifically assess sex differences, thus further investigations is warranted. As for the results reported here, there were no robust differences to note. For instance, two studies evaluated opioid self-administration following multiple intraperitoneal injections of ibogaine at identical doses, one involving female rats [42] and the other male rats [57], both demonstrating significant reductions in opioid self-administration under the specified conditions.

Mystical and psychological effects of psychedelics

The question of whether the psychogenic and subjective/hallucinogenic effects of psychedelics are necessary for their therapeutic effectiveness is a nuanced and central inquiry in psychedelic research [133]. While the psychedelic experience is characterized by profound alterations in perception, cognition, and consciousness, recent studies suggest that the therapeutic benefits may not be solely contingent on the intensity of these effects [134]. Some researchers propose that specific neurobiological mechanisms triggered by psychedelics, irrespective of the intensity of the psychogenic experience, underlie their therapeutic potential [134]. There is an alternative perspective, however, claiming that for psychedelics to exert an enduring effect, the subjective effects play a significant role, hence being necessary for their therapeutic effects [133]. For example, studies exploring alcohol or tobacco abstainers revealed persistent effects of psilocybin-facilitated treatment that extended well beyond the acute drug action [135, 136]. The findings indicated that greater mystical-type effects and more positive attributions regarding psilocybin sessions were associated with increased success in decreases in heavy drinking days or smoking cessation [135, 136]. Furthermore, ongoing investigations explore the possibility of developing non-hallucinogenic psychedelic analogs that retain therapeutic efficacy, shedding light on the ongoing question between psychogenic effects and therapeutic outcomes [137, 138]. Unraveling this intricate relationship is crucial for refining therapeutic approaches, maximizing the benefits of psychedelic-assisted treatments, and anticipating logistics around potential future implementation in the clinic. However, this is a debate that cannot be resolved in preclinical models.

Adverse events

The evidence found on psychedelic safety and tolerability is mainly on ketamine and ibogaine. The most consistent adverse effect associated with ketamine is dissociative effects [139, 140]. Past reviews in the use of ketamine for the treatment of depression have shown low rates of severe adverse effects; the main symptoms observed were psychomimetic, increase in blood pressure and heart rate, headache, muscle pain, and lower urinary symptoms [140, 141].

On the other hand, ibogaine's effect on cardiac physiology has been described, mainly causing a prolongation of QT. While clinical studies have predominantly demonstrated benefits in reducing opioid withdrawal symptoms and achieving cessation or reduced use in dependent individuals, there have been rare but notable reports of deaths attributed to cardiac arrhythmia [109], and respiratory arrest [102]. However, a recent study showed no severe cardiovascular or neurological adverse effects after administering a single dose [142]. Speculating on factors that could be at play in translational studies is important. For instance, pharmacokinetic variations between species, differences in metabolism, and the presence of comorbidities in human subjects could all contribute to discrepancies in the manifestation of adverse events. Furthermore, while 18-MC, which shares properties with ibogaine, is suspected to have even less neurological and cardiovascular influence [143], it is important to acknowledge that adverse event reports in preclinical studies are limited. This underscores the need for further research to elucidate the full spectrum of effects and risks associated with ibogaine and its analogs.

The additive potential of psychedelics

Studies investigating the addictive potential of some psychedelics are still scarce. Ibogaine is considered a Schedule 1 drug, according to the Drug Enforcement Administration [55], with no current accepted medical use. However, there is no robust evidence showing that ibogaine presents

a high potential for abuse [107]. Ketamine, on the other hand, is more commonly recreationally used, and evidence has shown some dependence potential when it is used frequently [107, 144–146]. The recreational use of ketamine has recently increased, with rarely reported fatal outcomes, but mostly related to related to aspiration of gastric contents [145]. Even though the potential for abuse of psychedelics was not evaluated in most of the preclinical studies, when place preference conditioning was tested along with the use of ketamine, it was found that the ketamine could induce a place preference on its own. This is consistent with studies in humans where the additive potential of ketamine has been observed, too [147].

Potential limitations and future directions

In the context of this preclinical scoping review, it is essential to note that our focus is primarily on traditional and hallucinogenic psychedelics and their potential applications in addressing OUD, except 18-MC, which was included due to its significance in the preclinical literature. While there is existing data on additional non-hallucinogenic psychedelics, such as tabernanthalog, our review has deliberately omitted their inclusion [137]. This decision is based in part on the fact that these substances do not possess the capacity to induce altered perceptions, which is a critical characteristic commonly associated with the term 'psychedelic' [32], and their potential applications in addressing OUD. We aimed to provide a comprehensive overview of the preclinical research landscape regarding potential benefits of psychedelics in the context of OUD. Thus, it would be worthwhile for future research to delve into the specific relationship between hallucinogenic effects and therapeutic outcomes. This avenue of inquiry may contribute to a deeper understanding of the nuanced interplay between psychoactive properties and therapeutic efficacy in the context of hallucinogenic psychedelics.

A notable limitation of our review is its exclusive focus on preclinical studies, which inherently constrains the generalizability of findings to clinical contexts. Moreover, acknowledging the absence of eligible studies on DMT, psilocybin, ayahuasca, and mescaline is a notable limitation in our review. To contribute to a deeper clinical understanding of those substances, exploring "street pharmacology" case studies [148], across various social media platforms could be suggested for insights into the therapeutic or aversive effects of these substances. This avenue presents a unique perspective that warrants consideration in future research efforts to enhance our understanding of the therapeutic potential and challenges associated with a broad spectrum of different psychedelics.

Conclusion

This scoping review evaluates the effectiveness of using psychedelics in preclinical models of opioid use disorder or opioid dependence. The analyzed papers demonstrate favorable results in reducing opioid use, treating withdrawal symptoms, and inhibiting opioid-conditioned place preference. The results show the importance of studying a broader range of compounds since there are different psychedelics like 4-AcO-DMT, DOI, and 18-MC that have not been studied in SUD studies with humans yet and, in this review, shown to be effective in animal models.

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Data availability Data will be provided upon reasonable request.

Declarations

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