Current perspectives on the clinical research and medicalization of psychedelic drugs for addiction treatments: Safety, efficacy, limitations and challenges

Psychedelics for the treatment of substance use disorders

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Abstract

Mental health disorders and substance use disorders (SUDs) in particular, contribute greatly to the global burden of disease. Psychedelics, including entactogens and dissociative substances, are currently being explored for the treatment of SUDs, yet with less empirical clinical evidence than for other mental health disorders, such as depression or post-traumatic stress disorder (PTSD). In this narrative review, we discuss the current clinical research evidence, therapeutic potential and safety of psilocybin, lysergic acid diethylamide (LSD), ketamine, 3,4-methylenedioxymethamphetamine (MDMA) and ibogaine, particularly in the context of the SUD treatment. Our aim was to provide a balanced overview of the current research and findings on potential benefits and harms of psychedelics in clinical settings for SUD treatment. We highlight the need for more clinical research in this particular treatment area, and point out some limitations and challenges to be addressed in future research.

Key points:

- Psychedelic-assisted therapies pose great potential for the treatment of substance use disorders, but more clinical research (randomized controlled trials [RCT] in particular) is still needed for this indication.
- Psychedelics have a good safety and tolerability profile when administered in supervised clinical settings, but better safety monitoring is advisable knowing that risks exist and could be higher in different settings.
- Future studies should address the limitations and challenges faced by most of this research, such as small sample sizes, difficulty in blinding, sample selection, safety monitoring, protocol variability and variability of effects.

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1. Introduction

Globally, in 2020, around 284 million people (aged 15-64 years) used illicit drugs, corresponding to ~6% of people in that age group [1]. Of these 284 million, approximately 38.6 million (~14%) had a substance use disorder (SUD), meaning they had impaired control over their drug use, it caused social impairment, included risky use, and/or they had pharmacologic dependence [1]. In the European Union (EU) and the United States of America (USA), approved medications are available for alcohol (e.g. acamprosate, naltrexone and disulfiram) and opioid use disorder (e.g., methadone and buprenorphine), but this is not the case for other SUDs [2]. Unfortunately, relapse rates are high among all SUDs; for instance, in the treatment of alcohol, tobacco and heroin use disorders, some studies have shown that more than 80% of individuals in treatment relapsed in one year [3] and similar relapse rates have been shown in cannabis and cocaine use disorders [4]. Drug use contributes substantially (1.3%) to all disability-adjusted life years (DALYs) worldwide, due to drug overdoses, accidents resulting from intoxication, perinatal complications, drug-related infectious diseases, cardiovascular diseases, hepatic diseases, cancer, and self-harm, among others [5]. Moreover, SUDs and other mental health disorders commonly co-occur, typically in ~50% of cases, which negatively affect the course and outcome of both [6].

Unmet treatment needs are high for SUD, but also for other mental health disorders, which affect >1 billion people worldwide and contribute greatly to global DALYs (4.9%) [7,8]. About a third of patients with anxiety disorders [9,10], depression [9,11], or psychotic spectrum disorders are regarded as treatment-resistant (not responding to two adequate doses and duration of medication) [9–11]. Therefore, therapies with better efficacy for (treatment-resistant) mental health patients are needed.

During the 1950s-60s, psychedelics showed promising results for treating a range of mental health disorders, including SUDs, anxiety and depression [12]. These classic serotonergic hallucinogens act primarily via activation of the neuronal 5-HT2A-receptors, and induce non-ordinary states of consciousness, thought, and feeling [13]. However, psychedelic research came to a halt in the 1970s for various reasons, including tighter regulation of pharmaceutical research, the failure of controlled clinical trials to live up to the expectations, and the pharmaceutical industry's lack of interest in funding clinical research on these molecules [14]. Adding to this, the USA Controlled Substances Act was signed into law by President Nixon in 1970, placing psychedelics into Schedule 1 (i.e., unsafe and high risk for abuse, with no accepted medical use for treatment); the United Nations international conventions [15] followed in the same vein. The past two decades have seen revived interest in psychedelics as treatments, and subsequently a rise in psychedelic research. In 2018-19, the US Food and Drug Administration (FDA) designated psilocybin as a “breakthrough therapy” for treatment-resistant depression and for major depressive disorder [16]. Recently, a phase-2 clinical trial evaluating the efficacy of psilocybin in treatment-resistant depression was completed [17], and following its positive results, phase III has started recruiting patients since the beginning of 2023. Besides treatment-resistant depression, the efficacy of psychedelics like psilocybin have been assessed for SUDs with promising results [18,19]. This renewed interest by researchers, patients, pharmaceutical companies, legislators, and the general public is not only limited to classic psychedelics, but applies to other psychedelic-related substances as well, including dissociatives (e.g., ketamine and ibogaine) and entactogens (e.g., 3,4-methylenedioxymethamphetamine [MDMA]) [20].

In response, several countries have adapted their legal frameworks to allow the therapeutic use of these substances. As with cannabis, whose medical use has been legislated in several countries in recent decades [21], Australia has already authorized the medical use of psilocybin

in depression and MDMA in PTSD, as unapproved therapeutic goods, under tight restrictions on the indications, on who can prescribe them (approved psychiatrists only) and the conditions under which they can be used, requiring the approval and oversight of an ethics committee [22,23]. Also, several states in the USA have (partially) decriminalised psilocybin and other psychedelics (e.g., in Oregon, psilocybin can be administered by a licensed facilitator without medical authorization) [16,24]. Other legislative changes in the use of psychedelics include medical use, clinical research, and policy analysis to evaluate the feasibility of decriminalisation or regulation of recreational use [16]. However, despite these broad legislative changes, to date only esketamine has received approval as treatment for a mental health disorder (i.e., treatment-resistant depression) by the FDA and the European Medicines Agency (EMA) [25]. No other psychedelics, dissociatives or entactogens have yet received such approval, although other phase III clinical trials have been recently finalized (e.g., MDMA for PTSD [26]) or are underway (e.g., psilocybin for depression [NCT05624268, NCT05711940, NCT06308653]).

In this narrative review, we discuss the clinical research, therapeutic potential (i.e., efficacy) and safety of psychedelics (including entactogens and dissociatives), particularly for the treatment of SUDs, a less-studied application of these drugs than other areas such as depression or PTSD. Previous reviews have focused on a single psychedelic substance or class [27], one specific SUD [28] or covered many different medical uses of psychedelics indications without looking in depth into SUDs [29]. By reviewing published clinical interventional studies (mostly randomized clinical trials with parallel-group or crossover designs and some single arm proof-of-concept studies) on psychedelic substances for the treatment of SUDs, available in PubMED up to late 2023, we aimed to provide a balanced overview of potential benefits and harms of psychedelics (including entactogens and dissociatives) in SUDs treatment, and point out some limitations and challenges to be addressed in future research.

2. Therapeutic effects

2.1. Psychedelic-assisted psychotherapy (PAP)

There are several psychedelic-assisted therapy (PAT) models, but most of the clinical trials on the therapeutic potential of psychedelics for mental disorders and addiction treatments published in the last two decades used the treatment model known as "psychedelic-assisted psychotherapy" (PAP) in any of its forms.

This treatment protocol varies from study to study depending on the psychedelic drug administered (Table 1) and the psychological intervention used, but generally combines a structured psychotherapeutic program with the administration of a psychedelic substance in just a few sessions, ranging from 1-2 sessions for psilocybin, 3-4 for MDMA, and up to 12 for ketamine [30] are done always under direct supervision of a trained therapist, who supports the patient in its aim to have an intense but safe psychedelic experience [31].

The PAP protocol usually consists of four different phases occurring on separate days: patient screening & assessment, patient preparation, psychedelic session and experience integration. In the screening & assessment phase, patients are evaluated to learn about their disorders and detect any latent psychiatric condition where psychedelics might be contraindicated, such as psychosis, bipolar disorder or schizophrenia. During the preparation phase, therapists build trust and rapport with the patient while preparing the psychedelic experience, setting an intention and instructing patients in relaxation techniques and other strategies for managing acute negative situations that might arise. During the psychedelic administration phase, the

patient receives the psychedelic substance in a well controlled environment and lays down in a couch or bed, with eye shades and headphones with a selected playlist for the entire duration of the acute psychedelic effects while they are instructed to stay introspective and be open to feelings, memories and thoughts arising [32]. The therapist or therapists are present to ensure safety and offer psychological support if needed. In the integration phase, usually happening a few days afterwards, the patient and the therapists go over the experience and work on it from a psychotherapeutic angle.

There is debate around the relative weight of the psychotherapy, the psychedelic substance and the subjective psychedelic experience in the therapeutic outcome, and whether PAPs are the most optimal therapeutic protocols for psychedelics. This has led to some new trial designs in the last years with minimal or none psychotherapeutic intervention to evaluate the efficacy of psychedelic with just safety support, but most of the studies referred in this review followed the classic PAP protocols.

2.2. Psilocybin

Psilocybin is the main psychedelic compound found in the *Psilocybe cubensis* mushrooms and other species from the *Psilocybe* family. When ingested, psilocybin is metabolised into psilocin, that is the psychoactive molecule primarily responsible for the psychedelic effects in the brain, mainly via the activation of the 5-HT2a serotonin receptor of the brain [13] and its neuroplastic effects [33].

Psilocybin is, along with MDMA and ketamine, among the three most-studied psychedelic compounds in the last two decades [30]; and its efficacy has been assessed in therapeutic settings for the treatment of depression, anxiety, existential distress and other conditions

following a life-threatening diagnosis. The efficacy of psilocybin has also been assessed along with conventional psychotherapy, as PAP, for the treatment of SUDs. Clinical studies have shown significant (Table 2) and lasting increases in abstinence and reductions of heavy drinking days in alcohol use disorder (AUD) patients after 2 administrations of psilocybin combined with Motivational Enhancement therapy or psychotherapy, with sample sizes ranging from 10 to 95 subjects, in open-label [34] and double blind [18] clinical studies, and also in 15 sessions of PAP combined with LSD sessions [35,36]. Studies on tobacco use disorder (TUD) showed increased and lasting abstinence after 2-3 psilocybin administrations combined with Cognitive Behavioural Therapy [19,37] in a small group of treatment-resistant tobacco smokers but without blinding or a control group. (Table 2)

Despite the promising results of these studies using PAP with psilocybin for the treatment of SUDs, these clinical trials have important limitations, mostly due to small samples and the lack of control groups in most cases. More RCTs with bigger samples would be needed to further evaluate the efficacy of this treatment for these conditions.

2.3. Dimethyltryptamine (DMT)

DMT or N, N-dimethyltryptamine is a psychedelic compound widely present in nature in many species of plants and animals, including in the brain of humans and other mammals [38]. As with other psychedelic compounds, it induces most of its psychedelic effects via activation of the 5-HT2a receptors in the brain [13]and increases neuronal plasticity [39].

When ingested orally, DMT is often coupled with monoamine oxidase inhibitors (MAOIs), to overcome the presence of MAO enzymes in the digestive tract in the human body [40]. The combination of plant leaves containing DMT (usually from *Psychotria viridis* or *Mimosa hostilis* species) and MAOIs (usually in the form of beta-carbolines from the *Banisteriopsis caapi* vine or the *Peganum harmala* plant) are referred as ayahuasca or yagé, traditionally used by many human groups from the Amazonian rainforest [40].

Ayahuasca has been explored in therapeutic settings with promising results for several mental health disorders and symptoms, including depression [41,42], social anxiety [43] and grief [44].

To date there have been no RCTs assessing the efficacy of Ayahuasca in SUDs. The only reports available include preclinical research and observational studies among healthy ritual ayahuasca users and patients with SUDs, reporting reductions in drug use, anxiety, and depression, and increases in quality of life and well-being [45]. However, these studies are out of the scope of this review and have major limitations, for instance, causality is impossible to determined in observational studies and the lack of standardization on ayahuasca doses, hampering conclusions about the potential efficacy [45], and therefore RCTs on DMT (alone or in ayahuasca form) for treatment of SUDs are warranted.

2.4. Lysergic acid diethylamide (LSD)

LSD is considered a classical hallucinogen and the most researched during the 1950s-60s [12]. It exerts its pharmacological effects mostly via activation of the 5-HT2a brain receptor [13] with the particularity of LSD acting for a longer time [46] and also acts as psychoplastogen by increasing neuroplasticity [39].

A meta-analysis including 6 clinical trials studying the efficacy of LSD in SUDs [47] found that a single dose of LSD had a beneficial effect on alcohol abstinence, which was significantly maintained in three of these studies 3 months post-treatment. Moreover, in one study with individuals with heroin use disorders, the effect was maintained up to 12 months post-treatment [48]. (Table 3).

These results show that LSD may have therapeutic potential for the treatment of alcohol use disorder; the effectiveness of this single dose was comparable to the positive effects of drugs commonly used for the treatment of alcohol use disorder such as naltrexone, acamprosate, or disulfiram [12,47]. However, some limitations are noted: The trials included were performed in the late 1960s with limited clinical research on LSD since then. Secondly, the individual studies included in the meta-analysis were underpowered and had methodological issues, including insufficient details on participant populations, limited diversity in LSD doses and treatment variables, the use of low-dose LSD as an active placebo in some trials, potential publication bias, blinding issues, and variations in outcome measures for alcohol use improvement [47]. In the context of the heroin study [42], the experimental design allows no meaningful inferences regarding the relative efficacy of LSD. In summary, the challenges in designing placebo-controlled and double-blind trials were underscored in these clinical studies, given ethical considerations and the inherent nature of the psychoactive intervention [11]. More robust designs are now needed to replicate or refute these findings and strengthen knowledge on the potential use of LSD for the treatment of alcohol and opioid use disorders.

2.5. 3,4-methylenedioxymethamphetamine (MDMA)

MDMA is a synthetic molecule that structurally resembles the hallucinogenic compound mescaline, and increases monoamine neurotransmitter levels in the brain, particularly serotonin, dopamine, norepinephrine [55] and hormones like oxytocin and vasopressin [56], resulting in a mood lift, closeness to others and increased sociability [57]. MDMA has shown positive results for the treatment of PTSD [58].

Two studies have assessed MDMA as a treatment for SUDs: Sessa et al. [57] explored the efficacy and safety of MDMA with psychotherapy as treatment for AUD, finding that MDMA was well tolerated, and participants reduced alcohol consumption at nine months post detoxification; however, this study lacked a control group and relied on retrospective self-report for alcohol use assessment, introducing limitations in assessing the specificity of MDMA's impact. Nicholas et al. [59] demonstrated the significant effectiveness of MDMA-assisted psychotherapy in reducing alcohol consumption in participants with severe PTSD and AUD compared to psychotherapy and placebo (Table 4). However, this study faced limitations such as narrow sample distribution of Alcohol Use Disorder Identification Test (AUDIT) scores, potential heterogeneity in reported substance use, and an exploratory nature hindering clinical interpretation, emphasizing the need for cautious interpretation of the results. Given the positive results observed in these studies [51, 53], there is a rationale for future investigations exploring the potential of MDMA-assisted therapy as an integrated treatment for co-occurring AUD and PTSD or AUD alone cases [53].

2.6. Ketamine

Ketamine is a dissociative NMDA-receptor antagonist from the arylcyclohexylamine family [60,61]. It is a well-established anaesthetic and analgesic, recently known for its use in

326 therapy for treatment-resistant depression (together with its enantiomer esketamine), with
327 possible applications for anxiety, suicidal ideation and bipolar disorder. Effects of use include
328 mild sedation, unusual thought content, confusion, delusions and hallucinations.

329 Ketamine has also been investigated in treatment for alcohol, cocaine and opioid use
330 disorders [61,62]. In their meta-analysis, Jones et al. identified seven completed clinical
331 studies of ketamine in addiction treatment; including two trials on cocaine use disorder, three
332 on opioid use disorder and two on alcohol use disorder, as well as several ongoing trials (on
333 alcohol use disorder) [62] (Table 5). Studies on cocaine use disorder showed that ketamine
334 increased motivation to quit cocaine and reduced craving; as well as reduction in frequency
335 and amount of cocaine use compared to midazolam and lorazepam [63,64]. Regarding
336 opioids, higher and frequent doses of ketamine treatment (compared to lower doses and less
337 frequent) increased abstinence rates and decreased craving [65,66]. Similar results have been
338 reported in alcohol use disorder, where ketamine treatment increased abstinence rates, time to
339 relapse, and reduced the likelihood of heavy drinking days compared to conventional
340 treatment and placebo [67]. Overall, treatment with ketamine has shown positive results in
341 addiction treatment, particularly in cocaine use disorder. Further research with larger samples
342 is needed, especially regarding Cocaine Use Disorder where maximum sample was n=20 and
343 Opioid Use Disorder (maximum sample n=70). Replication of these studies would be
344 beneficial. Other issues which need to be addressed include: active placebo use (midazolam,
345 lorazepam) in Cocaine Use Disorder research; comparison of different ketamine dose sizes
346 and amounts of the sessions (Opioid Use Disorder research); and the need to distinguish
347 ketamine assisted psychotherapy from ketamine alone (eg. Opioid Use Disorder research).
348 Considering the use of ketamine in addiction treatment, its own abuse potential should be
349 emphasized. Ketamine is strongly associated with club culture and widely used
350 recreationally, but limited evidence shows that in professionally controlled settings in patients

with treatment-resistant depression use of ketamine did not result in misuse or dependence [68].

2.7. Ibogaine

Ibogaine is an alkaloid substance from the tryptamine or indole family, isolated from the bark of the African shrub root *Tabernanthe iboga*. Its effects result from complex interactions between multiple neurotransmitter systems: as NMDA receptor antagonist, has affinity for opioid and serotonin receptors, and to monoamine transporters [72]. It has been hypothesised that ibogaine works by reversing the effects of opiates on gene expression and addictive loops and pathways in the brain, restoring neuroreceptors to their pre-dependent state [72].

A 2021 meta-analysis of studies included 24 studies on ibogaine [73]. Six clinical trials involved people with cocaine or opioid use disorders (Table 6). The four open-label trials showed reductions in opioid or cocaine withdrawal symptoms and craving, improved mood and depressive symptoms, all after ibogaine or noribogaine use [73]. One double-blind placebo-controlled clinical trial showed significant reduction in cocaine craving at 24 weeks compared to placebo [74], although the sample was very small (n=10). The second trial evaluated the effects of noribogaine in opioid-dependent patients compared to placebo, showing a trend to improved withdrawal ratings, but results did not differ significantly [75]. (Table 6).

Despite the big limitations of these studies using open designs, in most cases lack of blinding and placebo control, difficulty in blinding (use of normal placebo instead of active placebo), or a very small sample size (size range was only n=9-37), ibogaine appears to be a promising substance for future study, mostly in opioid withdrawal syndrome; along with ibogaine's

main (higher potency) metabolite, noribogaine [72,80], and ibogaine derivatives, 18-Methoxycoronaridine (18-MC) and tabernanthalog (TBG), which have a potentially more favourable safety profile [72,73]. Larger clinical trials are needed to assess the efficacy and safety of ibogaine.

3. Risks of psychedelic drugs

The studies discussed show that psychedelics have potential therapeutic value for the treatment of SUDs. However, it is important to be aware of the potential risks associated with the use of such substances, ranging from neurotoxicity to acute adverse psychological effects, and long-term mental health problems. Such risks to individuals can be expected to differ depending on the dose, frequency and context of use. Substances prescribed in medical settings aim to reduce or improve a certain symptom using the lowest and safest possible dose, using a certified quality product, in a highly controlled setting, for a limited period of time, while carefully monitoring the onset of potential adverse events. This clinical caution is an ethical imperative, but, as a result, there is a lack of published data finding acute or long-term risks of psychedelic use in clinical settings [81]. However, a lack of finding does not necessarily indicate a lack of risk, and therefore, to explore potential risks for these substances, we turn to data from studies of recreational psychedelic use to indicate issues that may arise, with the caveat that higher doses are commonly used, over greater periods of time and with less control over substance purity or contextual factors [82]. The risks identified can be grouped into risks for individuals (neurotoxicity, psychological adverse events, mental health consequences) and for public health. A full discussion of the public health risks of therapeutic psychedelic use is beyond the scope of this paper, but it is important to mention

398 the potential risks to society in passing: changes to public perception and consumption,
399 diversion of medical supplies to the recreational market, and issues of clinical oversight.

400 ### 3.1. Neurotoxicity

401 Neurotoxicity may be defined as any adverse effect on the structure or function of the central
402 and/or peripheral nervous system (by biological, chemical, or physical agents), that can
403 manifest at various levels, from individual neurons to entire regions of the brain, and can lead
404 to functional impairment or damage [83]. In preclinical trials, with doses higher than those
405 typically used in recreational and medical contexts, some psychedelics (i.e., ketamine,
406 ibogaine and MDMA) have shown some form of neurotoxicity (e.g., persisting serotonergic
407 damage with MDMA). Specifically, ketamine [84], ibogaine [85] and MDMA [86,87] have
408 shown this kind of toxicity at high doses and/or repeated administration. However, there is no
409 evidence of neurotoxic effects in humans at therapeutic doses [31]. On the other hand,
410 psilocybin, DMT and LSD were not found to induce neurotoxicity at high doses and/or
411 repeated administration [31], and some preclinical studies have shown that these compounds
412 may in fact induce neurogenesis and neuroplasticity [81].
413
414 The extent of the neurotoxicity of MDMA in therapy and its impact on neurocognitive tasks is
415 still debated; with research to date mostly based on preclinical research in animal models and
416 observational human studies with recreational MDMA users. Animal studies have shown
417 persisting serotonergic damage after MDMA exposure, but extrapolation to humans is limited
418 due to the lower dosing and frequency of recreational use [86,87]. Neuroimaging studies have
419 shown reduced serotonin transporter (SERT) binding in abstinent MDMA users, who also
420 showed deficiencies in a variety of biobehavioural processes with a serotonergic component:
421 deficits in sleep, mood, vision, pain, psychomotor skills, tremor, neurohormonal activity, and
422 mental status [88]. Recreational MDMA usage over time may cause haemodynamic and

electrophysiological alterations that show the use of increased resources for cognitive functions [89]. However, these findings are based on recreational use (i.e., higher doses, high frequency of consumption, adulteration, mixtures, etc. compared to therapeutic clinical use), and other confounders are difficult to rule out, like polydrug use, impurity, adulterants, and setting effects. A higher toxicity can be expected in typical party settings, as long periods of dancing can lead to increased body temperature, which exacerbates oxidative stress [86,90]. In addition, subtle cognitive and memory dysfunctions in MDMA users have been described. However, it is not clear whether these were related to MDMA use, or associated with other confounding factors, like sleep disruptions, prolonged stress or drug combinations [86].

Chronic ketamine use in humans has shown to result in grey matter depletion, specifically grey matter volume reduction in the left superior frontal cortex and right middle frontal cortex [91] and atrophy in some cortical areas of the brain [92]. Moreover, deficits in executive functions (worse scores and more time needed on tests) have been reported in people with ketamine dependence compared to non-user controls [91].

3.2. Physiological adverse effects

In medical settings modest blood pressure and heart rate increases have been reported with different kinds of psychedelics [93,94]. Consequently, patients with heart conditions should be screened and potentially excluded from psychedelic therapy [12]. It is worth noting that during one phase-3 MDMA clinical trial, no cardiac events (e.g., increased heartbeat) were reported with doses 80-180mg, and adverse events were more common in the placebo group [58]. In 9 MDMA studies which measured blood pressure, body temperature, and heart rate, all reported mild, transient, statistically significant elevations during the MDMA session, but none requiring medical intervention [95].

Using MDMA in recreational settings has been associated with adverse effects like bruxism, sweating, dry mouth, thirst, dizziness, insomnia and nausea. More dangerous adverse effects include accelerated heartbeat, hypertension, hyperthermia, hyponatremia and cardiac arrhythmia; and in extreme cases even death [96].

Patients with treatment-resistant depression who received ketamine (56 or 84 mg) expressed mild nausea, vertigo, dysgeusia, and dizziness symptoms compared to placebo [97]. Another study showed that oral ketamine (60, 120, 240 mg) did not increase blood pressure or heart rate compared to intravenous ketamine. Reducing and delaying ketamine's peak concentration by oral dosing with controlled-release ketamine tablets improved tolerability for patients with depression/anxiety [98]. Intensive recreational ketamine use can result in persistent bladder damage [99] and there are accounts of muscular damage in primates [100].

In clinical studies, nausea, ataxia and seizures have been reported from ibogaine administration at higher-than-recommended doses (four times the recommended dose of 25 mg/kg) [85]. No serious adverse events were reported in four open-label clinical trials [73], in normal doses (500, 600, or 800 mg), ibogaine was well tolerated by all participants [77]. Noribogaine resulted in headaches and nosebleeds as adverse events at normal doses [85]. There is a threat associated with ibogaine use and heart conditions, due to the potential prolongation of the QTc interval and torsades de pointes that could even cause death [85].

In recreational settings, most researchers consider classical psychedelics (LSD, psilocybin, DMT) as non-toxic in regular doses [81]. LSD in particular, exhibits very low physiological toxicity, even at very high doses, without any evidence of organic damage or neuropsychological deficits [12]. However, not all psychedelics have a good safety and tolerability profile, and lethal cases of some synthetic psychedelic phenethylamines use (e.g., NBOMe series: potent synthetic molecules like 25i-NBOMe, associated with significant health risks and often sold as LSD in illicit markets) have been reported [13]; although these are not being considered for therapeutic use yet.

Caution should be taken when using ayahuasca because of its MAO inhibitor components, which can cause serotonin syndrome or hypertensive crises when combined with certain medicines (e.g., psychostimulants or antidepressants) [101] or certain types of food (i.e., aged cheeses containing tyramine) [102].

3.3. Adverse effects on mental health

There is concern regarding the impact of psychedelics on mental health. In recreational settings, the most common adverse events experienced are psychologically difficult or challenging

487 experiences (so-called “bad trips”) [12], described as an acute state of confusion and dysphoria
488 that can lead to unpredictable behaviour in unsupervised environments [12]. In severe cases,
489 suicide attempts have been reported in people having these psychologically difficult or
490 challenging experiences; however, for a number of people these challenging experiences are
491 reportedly associated with beneficial outcomes afterwards [103]. People with previous
492 psychotic episodes or vulnerability to psychosis are at risk of increased psychotic
493 symptomatology during psychologically difficult or challenging experiences [12,103].
494 Variables such as drug dose, the degree of difficulty of the experience, the duration of the
495 experience, and the absence of physical comfort and social support increase the risk of having
496 a psychologically difficult or challenging experience [103]. Despite that, no potential negative
497 effects or risk to mental health were found among 19,299 participants of one study on
498 recreational psychedelic use (mainly LSD and psilocybin) [104]. These compounds may be
499 considered to have good safety and tolerability profiles when measures are taken to prevent
500 and mitigate severe symptoms and psychosis history [104]. Regarding MDMA, cases of
501 amnesia were observed only with high doses of the drug [105]. Ketamine users can experience
502 delirium, delusions, and confusion as part of its dissociative effect [60].
503
504 Under laboratory or supervised medical conditions, the risk of experiencing a psychologically
505 difficult or challenging experience is very low. In one study, less than 1% of the participants
506 (n=250) reported psychological distress or negative symptoms at psilocybin doses 20/70kg or
507 higher [103]. With DMT, patients reported mild adverse events such as anxiety, but resolved
508 after 30 minutes of the intravenous injection [93]. With respect to MDMA, only one study on
509 safety and tolerability has been performed in patients with AUD, and no unexpected adverse
510 events were observed among participants [57]. In the case of ketamine, feelings of dissociation
511 can be described as an adverse effect [97], but generally ketamine appeared to have a good

safety and tolerability profile in patients with PTSD and treatment-resistant depression [106]. Furthermore, ketamine did not exacerbate psychotic symptoms in patients with a history of psychosis, suggesting that the administration of ketamine in a clinical setting could also have a good safety and tolerability profile in those with psychotic history [107]. In all these cases, it should be noted that many participants in laboratory studies and some clinical studies have had prior experience with psychedelics, and adverse events are likely to be more common in inexperienced patients.

Some people report "flashbacks" after the use of psychedelics. This term is now considered a subtype of hallucinogen persisting perception disorder (HPPD), that refers to re-experiencing one or more of the perceptual effects induced by a hallucinogen at a later time, after the acute drug effects wear off [108]. The incidence of HPPD is very low and doesn't appear frequently with psychedelics used in therapeutic settings instead of recreationally – due to careful screening, preparation, supervision, and judicious doses of pharmaceutical quality drugs; but research in this area is inconsistent. One study reported 2% of subjects had "major perceptual changes" following therapeutic LSD use, but many of these studies were performed before operational criteria for HPPD were published in DSM-III-R, so they are difficult to interpret in the light of current diagnostic criteria [109].

Classic psychedelics do not seem to trigger addictive behaviour; indeed, sometimes they can even produce dysphoric effects [81]. For instance, LSD does not entail physical dependence as withdrawal syndrome, however, its frequent long-term use can lead to tolerance [12]. Classic psychedelics are not considered to be reinforcing, with no direct effects on brain dopaminergic systems, a circuitry that appears to play a crucial role in the transition to addiction [110]. Attempts to train animals to self-administer psychedelics have generally been unsuccessful

[13]. A similar phenomenon occurs with ibogaine, which also is described as non-addictive [79]. MDMA and ketamine are known to be addictive in recreational settings, although their addictive potential is described as lower than alcohol and tobacco - an expert delphic procedure conducted by Nutt et al. [111] rated the addictive potential of MDMA as 1.13, ketamine as 1.15, alcohol as 1.93 and tobacco as 2.21. In the case of MDMA, particularly high doses (> 3 mg/kg) could lead to addiction [105], as these doses are much higher than those used in therapy or in most recreational settings. Regarding ketamine use for addiction treatment, no studies have reported an illicit ketamine misuse after participants used it for the first time in a therapeutic context [61]. Despite the addictive potential of ketamine being well established in animal models, there is very limited evidence of this addictive potential happening in professionally controlled clinical settings [68]

4. Discussion

This article is a narrative review of the research on psychedelic drugs in clinical settings for the treatment of SUDs and the extent to which this research is proving to be efficacious and safe. Despite the positive results from most randomized clinical trials and other intervention clinical studies on the use of psychedelic assisted therapies for the treatment of SUDs presented in this review and the apparent low risk profile when used in clinical settings, many limitations and challenges need to be addressed by present and future research on this field.

4.1. Study limitations

The number of trials in this field is still limited and the samples used are small [112]. Most of the trials included in this review have demonstrated the efficacy of these drugs but only a small number of patients were included, which impairs the generalizability and validity of results, and highlights the need for new research using larger sample sizes and multi-center designs, as also described by Hovmand OR, et al [113]. Large sample sizes may not be a suitable idea for preliminary studies initially, but following a pilot study, larger size samples are the pathway to establish adequate reliability and validity of the findings. Many other factors affect the recruitment of larger samples, including the lack of funding, time constraints and ethical responsibility to minimise the risks and harms to the subjects.

Another associated limitation with sample size was the lack of control groups in some of the trials due to its preliminary or pilot design. There are a lot of reasons to justify the inclusion of a control group to establish efficacy. The effectiveness of a treatment should be demonstrated in comparison to control groups to discount the expectancy effect, placebo effect [114] and, in this case, to isolate and discount the impact of the classic psychotherapy component from the PAP intervention used in the study for a better assessment of the impact of the psychedelic component of the treatment. Also, to see if any possible risks or complications are due to the intervention, chance or a nocebo effect [114].

The selection of groups is another important limitation to prevent bias. There have been several studies that did not state the details of the recruited participants, such as demographic characteristics, prior experience with psychedelics, expectations and clear procedure that has been followed for sampling selection and randomization. It is very important to evaluate and consider these elements and to detail inclusion and exclusion criteria along with the

procedures that took place. Events occurring before the intervention and at each step of the study have the potential to influence treatment efficacy. Researchers' or subjects' own experiences with the intervention in the past are likely to influence the outcomes of the treatment in these clinical settings [115]. For instance, prior experience with psychedelics is likely to increase the expectancy and diminish the likelihood of negative experiences in study participants [116], and could also compromise the integrity of the blinding.

Psychedelic drug research is characterised by difficulty in blinding participants and this can lead to over-estimated effect sizes as result, due to de-blinding of participants and high response to expectancy [117]. While in almost all medical research standard practice is to use non-active placebo (eg. saline solution or glucose pills), this is insufficient in regards to psychoactive drugs - participants can easily distinguish placebo from the active compound and blinding would be unsuccessful. This is why in some psychedelic studies an active placebo is used (e.g., a lower dose of the psychedelic substance [17], a different psychoactive substance like methylphenidate [118], or a substance with some physiological noticeable effect like niacin [119]). However, by using an active placebo, blindness is still compromised in psychedelic trials, for which currently no perfect solution has been found but a few have been proposed [120].

Research on PAPs for SUDs often lacks long-term follow-up data, typically less than a year. This makes it challenging to determine if positive outcomes after psychedelic interventions are lasting or temporary, and if negative effects may arise in the long run. Short-term follow-ups have shown promising effects in reducing substance use and related symptoms, but there is a need for longer-term studies to confirm if these effects last. Studies with follow-ups

beyond a year are necessary to assess the sustainability of positive changes, risk of relapse and long-term safety.

Lack of exploration and understanding of mechanisms of action beyond the neurological/physical functioning, such as therapeutic alliance and other subjective factors is a significant limitation that needs to be further evaluated. Psychedelics are substances which increase sensitivity to environmental factors and their effect can highly depend on them [121]. The importance of setting is very well known among users of psychedelics, which cannot be overlooked in clinical trials. Interior design as well as music, lights, presence of other people, performing medical examinations, all affect the mood and thoughts of patients and can have an impact on results [122], but this is not well considered in most of the studies nor mentioned, and the extent of this influence is still under-studied.

4.2. Challenges

Despite these substances seem to pose low risks in well controlled clinical settings, adverse events in psychedelic trials are still poorly defined and not systematically assessed [123] For this, protocols and guidelines on safety monitoring need to be implemented, accessible and continuously updated with all the available information.

A broader discussion of the public health perspective is beyond the scope of this paper, but it is important to acknowledge that medicalization of psychedelics carries risk beyond the clinical

633 trials. For example, shifting public perceptions about the use of these drugs due to their legal
634 status may increase their use outside of healthcare settings, if people see the drugs as less
635 harmful than previously perceived. This could also result in increased risky behaviours and
636 increased recreational or self-administered usage. For instance, microdosing, or the
637 consumption of sub-perceptual doses of psychedelics regularly is a trend increasing globally
638 [124], as is the recreational use of a range of psychedelic drugs, most notably ketamine and
639 psilocybin [125].
640
641 Although the research on the clinical use of these drugs demonstrates a good safety and
642 tolerability profile, the recreational use or any use outside of research or healthcare settings,
643 carries additional risks, such as those associated with contaminated or inconsistent products
644 found in illicit markets [126], comorbid health conditions and other factors which are not
645 examined in clinical trials. For this reason, further research is needed to better understand the
646 mechanisms and safety profile of psychedelics in clinical contexts and outside of them.
647
648
649 **4.3. Future directions**
650
651 This is an important area for future research and development from an addiction treatment
652 perspective, but much needs to be done to ensure the safety of these drugs prior to any
653 conclusions being drawn, and to improve the quality and validity of any conclusion that
654 might drive the future implementation of these treatments. Addressing the limitations and
655 challenges of psychedelic research in a rigorous manner is key for the future of the field,
656 especially in the light of the problems that undermined psychedelic research in the past [127].
657

Despite the promising results from recent clinical trials mentioned in this narrative review, further research is needed to safely advance on the path of medical use of psychedelics for treatment of SUDs and other mental conditions. For this to happen, it would be very beneficial to have support from public entities in the form of funds to speed up the research process and by establishing rational legislative frameworks [128]; a conventional, commercial, patent-based pharmaceutical approach alone may not be enough for a complete development and implementation of such therapies in the best way possible.

Most of the aforementioned substances (Psilocybin, DMT, LSD, MDMA) are listed as Schedule 1 in the UN 1971 Convention on Psychotropic Substances, which results in costly and time-consuming bureaucratic processes to perform both preclinical and clinical studies with these drugs, prompting a number of researchers to suggest reclassification to facilitate research and development in this area. Another reason for reclassification is that the Schedule 1 category, by definition, should contain substances with no known therapeutic effects, a high potential for abuse/dependence, and evidence of serious adverse effects, which, it can be argued, does not to apply to the psychedelics, entactogens and dissociatives discussed here. Reclassification can also reduce stigma associated with the use of these drugs [129] leading to a decrease in harm and an increase in research interest in this field.

It is also important to make psychedelic therapies accessible and feasible for implementation once their effectiveness and safety are proven. This can be a challenge; most protocols describe a series of preparatory sessions prior to the session where the substance is administered, followed by the integration sessions, which may extend safety and efficacy, but also duration of treatment and costs, and reduce adherence. In less developed countries there can be bigger financial barriers in access to these medications [129]. More comprehensive reporting and

683 evaluation of these methods could help to develop best practice guidance and policies in this
684 field.

685

686 Despite the urgent need for innovative new treatments to address the epidemic in mental
687 health disorders, the implementation of such new therapies remains a challenge [128,130].
688 There is a need for the issue to be addressed as early as possible, taking into consideration
689 that several psychedelics researched are in Phase II-III of clinical trials and close to medical
690 authorization if not already authorized, as with esketamine. Australia's authorization for
691 strictly controlled medical use [23] and some states in the USA [24] are examples of how
692 quickly changes could happen outside of the regular paths of clinical research and medicine
693 authorization, highlighting the need to put in place measures to reduce the impact on public
694 health of changes in popularity and availability of these substances.

695

696 **5. Conclusion**

697 Studies on psychedelic therapies such as PAPs for the treatment of SUDs show promising
698 results in efficacy and safety so far. This is an important area for future research and
699 implementation, and one which has seen a renewal of interest in recent years, but so far has
700 produced fewer studies and publications than the use of PAPs for other conditions such as
701 depression or PTSD. There is great potential for the use of psychedelics in the treatment of
702 SUDs, but more detailed and rigorous research is needed to further expand clinical and
703 academic understanding of this area and allow for effective and safe development of these
704 treatments (if finally proven efficacious and safe).

705

For instance, there are still significant challenges and limitations inherent to this research field which need to be addressed, such as small sample sizes, difficulty in blinding, sample selection, the standardisation and homogenization ofPAP protocols across different studies, safety monitoring and very variable effects among different individuals and settings. Research method standards in this area need to be rigorously upheld, to avoid overestimating or overstating the use of these substances in the face of strong public opinion. Effectiveness and adverse effects must be properly assessed and monitored with high quality studies, such as RCTs, big samples, longer follow-ups and carefully chosen study variables, measurements and protocols. Also regulatory measures should be taken to facilitate this research, while ensuring the safety of this treatment methodology.

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Table 1: Classes, doses, duration and main targets of the psychedelic compounds evaluated in this review.

Substance	Class	Dose	Duration	Main target
Psilocybin	Classic Psychedelic	25-30 mg (orally)	4 to 6 hours	5-HT2A receptors (agonist)
LSD	Classic Psychedelic	100-200 ug (orally)	12 hours	5-HT2A receptors (agonist)
DMT/Ayahuasca	Classic Psychedelic	96-160 mg DMT and 25-42 mg harmine (orally)	4 hours	5-HT2A receptors (agonist), MAO (inhibitor)
MDMA	Empathogen-entactogen Psychedelic	120 mg (orally)	4 hours (redosing 1 or 2 times is a common practice to extend effects in PAP)	Monoamine releasing agent
Ketamine	Dissociative Psychedelic	0.41 - 0.71 mg/kg (intravenous infusion), 2-2.5 mg/kg (intramuscular)	2 hours	NMDA receptors (antagonist)
Ibogaine	Dissociative Psychedelic	500-1800mg, 8–12 mg/kg (orally)	up to 72 hours	NMDA receptors (antagonist), kappa-opioid receptor (agonist)

DMT: Dimethyltryptamine, kg: Kilogram, LSD: Lysergic Acid Diethylamide, MAO: Monoamine Oxidase, MDMA: 3,4-Methylenedioxymethamphetamine, mg: Milligram, NMDA: N-Methyl-D-Aspartate

Table 2: Studies of psilocybin for substance use treatment

Disorder	**Type**	**Authors**	**Main findings (Primary outcome)**

Alcohol use disorder (AUD)	Open label single group study (NCT01534494)	Bogenschutz et al. [34]	After 10 subjects with AUD received two psilocybin-assisted therapy sessions (0.3 mg/kg and 0.4 mg/kg) combined with 12 weeks of Motivational Enhancement Therapy, percent heavy drinking days from week 5 to 12 decreased relative to baseline (mean difference (SD) = 26.0 (22.4), 95% CI 8.7–43.2, p = 0.008).
Alcohol use disorder (AUD)	Double-blind active-placebo trial (NCT02061293)	Bogenschutz et al. [18]	Two psilocybin administrations (25 mg/70 kg and 25-40 mg/70 kg) in combination with psychotherapy reduced percentage of heavy drinking days compared to active placebo (diphenhydramine) and psychotherapy at 32-week (9.7% vs. 23.6%, respectively; mean difference 13.9%; (95% CI, 3.0-24.7; Hedges g = 0.52; p = .01), with a sample size of 95 participants with AUD.
Alcohol Use Disorder (AUD)	Open label single group study	Rydzyński et al. [35,36]	31 men with AUD, underwent a mean of 15 sessions of PAP with 6–30 mg and LSD 100–800 μg (mean 12 sessions). After a mean follow up of 6 years, 32% (10/31) became totally abstinent, 32% (10/31) was abstinent from alcohol for 6–12 months, and 58% (18/31) of patients had a "satisfactory therapeutic effect" undefined by the authors.
Tobacco use disorder (TUD)	Open label single group study	Johnson et al. [19,37]	After 2 doses of psilocybin (20 mg/70 kg and 30 mg/70 kg) combined with Cognitive Behavioural Therapy, 12 of 15 participants (80%) showed seven-day point prevalence abstinence at 6-month follow-up, assessed by smoking biomarkers and self-report measures.

	(NCT01943994)		10 participants (67%) were abstinent at 12-month follow-up, 9 participants (60%) were abstinent after 30 months.

AUD: Alcohol Use Disorder, CI: Confidence Interval, kg: Kilogram, mg: Milligram, µg: Microgram, NCT: National Clinical Trial, p: p-value, PAP: Psychedelic-assisted Psychotherapy, SD: Standard Deviation, TUD: Tobacco Use Disorder

Table 3: Studies of LSD for substance use treatment

Disorder	Type	Authors	Main findings (primary outcome)
Alcohol use disorder (AUD)	Double-blind placebo trial	Smart et al. [49]	No significant intergroup differences were found in drinking history and % change in time abstinent at 6 months follow-up (OR: 1.41; CI: 0.36-5.60) between the LSD group (800 µg; n=10) vs the placebo (60 mg ephedrine; n=10) vs the no drug group (n=10)
Alcohol use disorder (AUD)	Double-blind active-placebo trial	Hollister et al. [50]	Maintained abstinence based on the Drinking Behaviour Interview at 2 months follow-up (OR: 2.27; CI: 0.87-5.94) but not at 6 months follow-up (OR: 1.70; CI: 0.61-4.71) in the LSD group (600 µg; n= 36) compared to the active placebo group (60 mg d-amphetamine; n= 36)
Alcohol use disorder (AUD)	Double-blind placebo trial (LSD single dose vs no drug)	Ludwig et al. [51]	LSD group (210 µg; n= 132) was not superior to the no drug group (n= 44) at 1-month follow-up (OR: 1.88; CI: 0.93-3.81) in abstinence rates

Alcohol use disorder (AUD)	Double-blind active-placebo trial	Bowen et al. [52]	LSD group (500 µg; n= 22) did not show significant differences in abstinence rates at 12-months follow-up (OR: 1.48; CI: 0.43-5.10) compared to active placebo group (25 µg LSD; n= 22)
Alcohol use disorder (AUD)	Double-blind active-placebo trial	Pahnke et al. [53]	Significant improvement in Global Adjustment and Drinking Behaviour for LSD group (450 µg; n= 73) at 6-months follow-up (OR: 2.08; CI: 0.94-4.60) compared to the active placebo group (50 µg LSD; n= 44)
Alcohol use disorder (AUD)	Double-blind placebo trial	Tomsovic & Edwards [54]	Maintained abstinence and beneficial effect in the Drinking Adjustment Scale at 3 months follow-up (OR: 2.25; CI: 0.99-5.10) in the LSD group (500 µg; n= 52) compared to treatment as usual (n= 45)
Heroin use	Double-blind placebo trial	Savage & McCabe [48]	Significant lower rate of relapse in the LSD group (300-450 µg; n= 36) compared to the no drug group (n= 37) at 3, 6, 9 and 12 months post-treatment (X2=3.86; p.<0.5). Twelve of the 36 subjects in the treatment group (or 33.3%.) maintained total abstinence for at least one year as opposed to two (5%) of 37 in the control group (P<.05).

AUD: Alcohol Use Disorder, CI: Confidence Interval, LSD: Lysergic Acid Diethylamide, µg: Microgram, n: Sample Size, O.R.: Odds Ratio, p: p-value, SD: Standard Deviation

Table 4: Studies of MDMA for substance use treatment

Disorder	Type	Authors	Main findings (primary outcome)

Alcohol use disorder (AUD)	Open-label safety and tolerability proof-of-concept study	Sessa et al. [57]	The MDMA-assisted therapy post-detox group (187.5+187.5 mg; n= 14) showed a decrease in the average units of alcohol consumption from 130.6 units per week before detoxification to 18.7 units per week 9 months after the detoxification.
Alcohol and substance use	Randomized single-blind controlled trial (MDMA vs placebo)	Nicholas et al. [59]	The 3-session (120+180+180 mg) MDMA-assisted therapy group (n= 42) showed greater reduction in AUDIT scores from baseline to study termination compared to the placebo + therapy group (n= 40) (F= 4.20, p = 0.0436; Hedge's g= .45).

AUD: Alcohol Use Disorder, AUDIT: Alcohol Use Disorder Identification Test, mg: Milligram, n: Sample Size, p: P-value

Table 5: Studies of ketamine for substance use treatment

Disorder	**Type**	**Authors**	**Main findings (primary outcome)**
Cocaine Use Disorder	Double-blind midazolam-controlled clinical trial (NCT02596022)	Dakwar et al. [63]	Ketamine infusion (0.71 mg/kg) led to significantly less cocaine use compared to midazolam: 1.61 vs. 4.33 choices of cocaine in self-administration test, (n=20, $p < 0.0001$).
Cocaine Use Disorder	Double-blind lorazepam-controlled clinical trial (NCT01790490)	Dakwar et al. [64]	Compared with lorazepam (n=3), a single ketamine infusion (0.71 mg/kg, n=5) led to a mean 3.9-point gain in University of Rhode Island Change Assessment (motivation to quit cocaine assessment) (p = 0.012), which

			corresponds to an approximately 60% increase over preceding values.
Opioid Use Disorder	Randomized controlled trial	E. M. Krupitsky et al. [66]	At one-year follow-up: significantly higher rate of abstinence in the multiple ketamine group (3 sessions) compared to a single group. 50% in the multiple group (n=26, 2.0 mg/kg i.m.) remained abstinent, compared to 22.2% of subjects (n=27) in the single ketamine group ($p < 0.05$)
Opioid Use Disorder	Double-blind randomized clinical trial	E. Krupitsky et al. [65]	Higher dose of ketamine (2.0 mg/kg i.m., n=35) produced a significantly greater rate of abstinence within the first two years of follow-up, and a greater and longer-lasting reduction in craving than did low dose ketamine (0.2 mg/kg i.m., n=35) (almost all months of follow-up: $p < 0.05$ and $p < 0.01$)
Opioid Use Disorder (opioid withdrawal symptoms)	Randomized, placebo-controlled, double-blind clinical trial	Jovaisa et al. [69]	Ketamine group (0.5 mg/kg/h, n=22) presented better control of withdrawal symptoms, which lasted beyond ketamine infusion itself, had lower cortisol level ($p<0.05$) and used a lower total clonazepam dose ($p<0.001$) compared to control (n=28)). Abstinence rates after 4 months follow-up between groups differed insignificantly.
Alcohol Use Disorder	Controlled clinical trial (no	E. M. Krupitsky	Total abstinence for more than one year was observed in 66% of patients in the ketamine group (2.5 mg/kg, i.m., n=111),

	placebo, no randomization)	& Grinenko [70]	compared to 24% of the conventional treatment control group (n=100) (p < 0.01)
Alcohol Use Disorder	Double-blind placebo-controlled phase 2 clinical trial (NCT02649231.)	Grabski et al. [71]	Ketamine group (0.8 mg/kg i.v., n=48) showed significantly greater number of days abstinent at 6-month follow-up (mean difference=10.1%, 95% CI=1.1, 19.0) than placebo group (n=48). There was no significant difference in relapse rate between the ketamine and placebo groups.
Alcohol Use Disorder	Double-blind midazolam-controlled pilot trial (NCT02539511.)	Dakwar et al. [67]	Ketamine (0.71 mg/kg) significantly increased the likelihood of abstinence, delayed the time to relapse, and reduced the likelihood of heavy drinking days. 75% of participants in the ketamine group (n=8) reported abstinence, compared with 27% in the midazolam group (n=11).

CI: Confidence Interval, i.m.: Intramuscular (a route of administration), i.v.: Intravenous (a route of administration), kg: Kilogram, mg: Milligram, NCT: National Clinical Trial, n: Sample Size, p: P-value,

Table 6: Studies of ibogaine for substance use treatment

Disorder	**Type**	**Authors**	**Main findings (primary outcome)**
Opioid Use Disorder	Phase 1 open-label clinical trial (Noribogaine)	Geoffroy P, [76]	Mean SOWS (Subjective Opiate Withdrawal Scale) score at baseline in n=9 subjects was 30.3. It declined to 10.4 51 hours post loading dose (loading dose was

			80mg, followed by next doses. Mean cumulative dose was 653 mg).
Opioid and Cocaine Use Disorder	Open-label clinical trial (Ibogaine)	Mash et al. [77]	Desire to use and intention to use opiates were significantly lower ($p<.0001$) compared to pre-ibogaine treatment and post-treatment. Ibogaine doses were 500, 600, or 800 mg. Regarding cocaine, results were not significant. n=27.
Opioid Use Disorder	Open-label clinical trial (Ibogaine)	Mash et al. [78]	Objective Opiate Withdrawal Scale (OOWS) score was significantly higher in subjects (n=32) pre-ibogaine treatment and 12h post the last opiate dose (mean=6) compared to post-treatment with ibogaine (800mg). 12h after ibogaine treatment mean OOWS score was 1 and 24h after ibogaine treatment mean OOWS was 2. $p<0.05$.
Opioid and Cocaine Use Disorder	Open-label clinical trial (Ibogaine)	Mash et al. [79]	Subjects (n=37) undergoing opioid detoxification reported significantly decreased drug craving on five measures taken from the heroin craving questionnaire (HCQ-29) post-treatment with ibogaine (8–12 mg/kg) and 1 month follow-up assessments compared to baseline measures ($p < 0.0001$).
Cocaine Use Disorder	Double-blind placebo-controlled clinical trial (Ibogaine)	Prior & Prior, [74]	There was significant reduction in severity of symptoms of cocaine withdrawal in subjects in ibogaine group (n=10, 1800mg of ibogaine) (MCCS score intensity at time zero = 7,4 ± 0,70 ; intensity at time 72 h = 2,6 ± 0,84 ; $p< 0,0001$, and a statistically

			significant improvement between the ibogaine group at time 72 hours and at 24 weeks (p = 0,0047)). No such improvement was observed in the placebo-controlled group (n=10).
Opioid Use Disorder	Double-blind placebo-controlled clinical trial (Noribogaine)	Glue et al. [75]	Non statistically significant trend toward decreased total score in opioid withdrawal ratings. Ibogaine dose was 60, 120 and 180 mg, ibogaine group: n=18, placebo group: n=9.

HCQ-29: Heroin Craving Questionnaire-29, kg: Kilogram, mg: Milligram, MCCS: Modified Cocaine Craving Scale, n: Sample Size, OOWS: Objective Opiate Withdrawal Scale, p: P-value, SOWS: Subjective Opiate Withdrawal Scale