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Psychedelic-assisted research for the treatment of drug and alcohol addiction

A scoping review

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Master thesis in Public Health Science

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The Norwegian University of Life Sciences (NMBU)

Preface

This is a master thesis concerning public health science, delivered within the faculty of Landscape and Society (LANDSAM) at the Norwegian University of Life Sciences (NMBU). The thesis is structured as a scoping review with a journal article and a supplementary "kappe". The kappe was used to draw more context around the topic by including biological info and details from the studies included for this review. The kappe was also used to shed light on its relevance to public health and how knowledge acquired through new research can be useful tools or solutions in addressing public health problems. The reviews relevance to the public health situation in Norway was also highlighted, and propositions for future research, in Norway or elsewhere.

Working on this thesis has been an interesting and exciting project from start to finish. It has been a steep learning curve and challenging process, but the rewards outweigh any negative aspects. It brings great joy to be able to work on such interesting and important subjects, and to get the chance to conduct literature searches and contribute with research on my own.

I would like to thank my supervisor, Fiona Vande Velde, for giving such great guidance and feedback, and for providing a steady stream of ingenious tips and recommendations along the way. You have been a steady and reliable rock, always ready to soothe any nerves or uncertainties.

Lastly, I would like to thank the university with all its teachers and fellow students, and my family and friends, who have supported me throughout my education.

Susanne Ranheim Berg

Ås, 16.05.2022

Sammendrag av artikkel

Denne masteroppgaven er skrevet som en scoping review artikkel med en tilhørende «kappe» for mer omfattende informasjon, detaljerte forklaringer og data som supplement for artikkelen.

Introduksjon: Det har blitt økt interesse for bruk av psykedelika i behandling av en rekke ulike psykiske lidelser. Blant disse er avhengighet til alkohol eller andre narkotiske stoffer, som har begrenset med behandlingstilbud for de som opplever liten effekt av konvensjonelle behandlingsalternativer. Denne scoping review artikkelen vil kartlegge den nåværende forskningsstatusen og identifisere relevante studier som bruker de psykedeliske stoffene LSD, psilocybin, MDMA og ketamin i behandling av avhengighet til alkohol eller narkotiske stoffer. Disse vil brukes til å fremlegge strategier for fremtidig forskning basert på retningslinjer for sikkerhet, standarder og strategier som er utarbeidet etter evaluering av tidligere forskning med psykedelika.

Metode: Det ble utført systematiske litteratursøk i fire databaser (Ovid Medline, Embase, Scopus og Web of Science) i tillegg til søk i ekstra bibliografier, siteringssøk og online søk. Alle resultater ble lastet opp til EndNote for gjennomgang av titler, abstrakter og avslutningsvis studier i full-tekst for å vurdere valgbarhet basert på inklusjons- og eksklusjonskriteriene. De inkluderte studiene var begrenset til de som anvendte de utvalgte psykedeliske stoffene for å behandle en avhengighet til alkohol eller narkotiske stoffer, i en terapeutisk eller klinisk setting med et adferdsrelatert studieutfall eller terapeutisk gevinst. Det ble brukt et pilot-testet skjema for ekstraksjon og kartlegging av data, som ble organisert og presentert i relevante tabeller.

Resultater: Det ble identifisert 19 studier innenfor avgrensningene til denne artikkelen, en med LSD, MDMA og psilocybin, og 16 med ketamin. Det er bemerkelsesverdige metodologiske forskjeller mellom de inkluderte studiene, i tillegg til at de fleste ikke har publisert tilstrekkelig med data og materiale for å kunne evaluere eller replikere studiene. Det er stor variasjon i egenskapene til studiene og deltakerne, samt variasjon i kombinasjoner av intervensjoner og psykedeliske stoffer som er brukt i de ulike studiene. Studieutfall for avholdenhet og endringer i rus-begjær er signifikant i de fleste studiene, spesielt de kontrollerte.

Konklusjon: Denne scoping review artikkelen har fremhevet den nåværende forskningsstatusen for psykedelika-assistert behandling av avhengighet. Det ble identifisert mest forskning med ketamin. De inkluderte studiene presenterte lovende resultater og positive utfall, på tross av metodologiske forskjeller mellom studier. Slike forskjeller og andre begrensninger kan minimeres ved bruk av retningslinjene, standardene og strategiene presenter i denne scoping review artikkelen.

Nøkkelord: Avhengighet, psykedelika, hallusinogener, avhengighetsbehandling, terapi, kliniske studier.

Article abstract

This master thesis is written as a scoping review article supplemented with a “kappe” for more extensive information, detailed explanations, and supplementary data for the article.

Introduction: Psychedelic-assisted treatments are receiving renewed interest for treating a range of different mental health disorders. Among these are addiction disorders, which have limited treatment options for people who experience little effect of conventional treatments. Due to the relatively new application, this review will scope the field of relevant studies utilizing the psychedelic substances LSD, psilocybin, MDMA, and ketamine for treating addiction disorders, to map the current research situation and inform strategies for future research, using safety guidelines, standards, and strategies proposed in reviews of previously conducted psychedelic research.

Method: Systematic literature searches in four databases (Ovid Medline, Embase, Scopus, and Web of Science) were performed, in addition to handpicked searches through citation tracking, additional bibliographies and online searches. All results were uploaded to EndNote 20 for screening of titles, abstracts, and lastly in full text to assess eligibility according to the eligibility criteria. The included studies were limited to those utilizing the selected psychedelic substances treating addiction disorders in a therapeutic or clinical context with a behavioral outcome or therapeutic gain. A pilot tested data charting tool was used to extract relevant data, which were presented in relevant tables.

Results: Nineteen studies were identified within the limitations set for this review, one investigating LSD, one MDMA, one psilocybin, and 16 ketamine. There are noteworthy methodological differences, and the majority of studies do not provide sufficient data and materials to adequately evaluate and replicate the trials. Study and participant characteristics vary greatly, as does the different combinations of interventions and psychedelic substances applied in the studies. Overall, abstinence rates and changes in craving are significant in most studies, especially in the controlled studies.

Conclusion: This review highlighted the current research status investigating psychedelic-assisted addiction treatments, identifying most research investigating ketamine. Overall, the included studies showed promising outcomes, but there are noteworthy methodological

differences between the studies, and limitations that can be addressed using safety guidelines, standards, and strategies presented in this review.

Keywords: Addiction, psychedelics, hallucinogens, addiction treatment, therapy, clinical trials.

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List of abbreviations

5HT2A-receptor – 5-hydroxytryptamine receptors 2A

AC – Addiction counseling

AE – Alcohol education

AT – Aversion therapy

AUD – Alcohol use disorder

AUDIT – Alcohol use disorder identification test

AWS – Alcohol withdrawal symptoms

CBT – Cognitive behavioral therapy

CRPS-I - Complex regional pain syndrome type 1

CUD – Cannabis use disorder

DMT – N,N-dimethyltryptamine

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition

EHS – Environment, health, and safety

FDA – Food and Drug Administration

ICD-10 – International Classification of Diseases, 10th edition

ICU – Intensive care unit

IM – Intramuscular

IV – Intravenous

JBI – Joanna Briggs Institute

Ketamine – Ketamine hydrochloride

KPT – Ketamine-assisted psychotherapy

LSD – Lysergic acid diethylamide

MAPS – Multidisciplinary association for psychedelic studies

MBRP – Mindfulness-based Relapse Prevention

MCDA – Multicriteria decision analysis

MDD – Major depressive disorder

MDMA – 3,4- methylenedioxymethamphetamine

MET – Motivational enhancement therapy

MRI – Magnetic resonance imaging

MRM RET – Maladaptive reward memories retrieval

NAc – Nucleus accumbens

NMDA-receptor – N-methyl-D-aspartate receptor

NSD – Norsk senter for forskningsdata

OT GA – Opioid tapering under general anesthesia

OUD – Opioid use disorder

PT – Psychotherapy

PTSD – Post traumatic stress disorder

REK – Regionale komiteer for medisinsk og helsefaglig forskningsetikk

rTMS – Repetitive transcranial magnetic stimulation

SPECT – Single-photon emission computer tomography

SUD – Stimulant use disorder

TIMBER – Trauma interventions using mindfulness-based extinction and reconsolidation of memories

TRD – Treatment resistant depression

VTA – Ventral tegmental area

WHO – World Health Organization

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Kappe

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1.0 Introduction

The medical application of psychedelic substances has received renewed interest in the past decades for its potential use in therapies for treatment-resistant mental health disorders such as alcoholism or drug addiction, anxiety, depression, schizophrenia, and post-traumatic stress disorder (PTSD) (Perkins et al., 2021). As a group, psychedelic substances are versatile with several mechanisms of action that make them relevant and beneficial in several treatment contexts for disorders that also affect the brain and body in different ways. This means that in addition to treating different addictions such as addiction to tobacco and alcohol, the same substances can also be investigated for life-ending depression and anxiety, schizophrenia, or even an anesthesia at large doses (Johnson et al., 2014; Kolp et al., 2014; Krebs & Johansen, 2012; Nigam & Pandurangi, 2021; Penn et al., 2021).

Preliminary research to treat substance abuse with psychedelic substances showed superior results in regards to abstinence (Krebs & Johansen, 2012; Nigam & Pandurangi, 2021), with continued research using animal models confirming their implication in addiction treatments (Alper et al., 2018; Katsidoni et al., 2011; Vaidya et al., 1997). It is however unclear how far this research has come, and a scoping review will therefore be performed to further explore what disorders have been under investigation and with which substances. This will shed light on the current research landscape and inform future action.

1.1 Addiction as a global health problem

The World Drug Report of 2021 showed an increase in the use of alcohol, cannabis, pharmaceutical opioids, and sedatives, as reported by addiction medicine professionals in most countries in the world (UNOCD, 2021). The World Health Organization (WHO) estimates that around 35 million people are suffering from a drug addiction and that over 180 thousand deaths could be directly linked to drug use in 2019 (UNOCD, 2021; WHO, n.d.).

Opioid dependency has become a growing problem worldwide, especially in the US, estimating that around 123 thousand deaths were contributed by opioids in 2019. Unfortunately, only about half of the countries in the world have methadone available as a treatment option for those struggling with opioid dependence (WHO, n.d.). Therefore, researchers and medical practitioners have voiced a need for new and improved medical treatments for a range of mental health disorders, including addiction, that lack available medicine or treatment options for those resisting treatment (Belouin & Henningfield, 2018).

1.2 Public health relevance

In Norway we estimate that around 8% of men and 3% of women have a dependency to alcohol – a condition that is becoming evidently more common among young people (age 18-35), and especially men (Skogen et al., 2018). There is also evidence of correlation between higher education and income, and an increase in alcohol consumption – yet there are few in this socioeconomic group presenting with alcohol or drug dependency problems. Addiction, and the physical, mental, social, and economic problems that frequently follows, seems to be more prominent among those with low socioeconomic status. This also means that the disorder is more frequent among those with limited means to seek out and complete treatments for their disorder (Skogen et al., 2018).

For other illicit drugs, we see an increase in dependency on a global scale, but we lack sufficient data from the Norwegian population to evaluate this properly. The distribution of prescription pharmaceuticals has been steady in the period 2004 to 2015, at least not indicating an increase in misuse of prescription drugs (Skogen et al., 2018).

In 2020 there were 386 alcohol-related deaths in Norway, a small increase from 335 in 2018. Still, alcohol-related deaths have decreased by 25% from 1996 to 2018, which is a clear decline when compared to the population growth – especially among men (Skogen et al., 2018). Drug-related deaths (overdoses) increased exponentially from 1996 to 2001, then declined until 2003, where it stabilized. Then in 2020, there were 324 drug-related deaths registered in Norway, the highest number since 2001. Around 80% of overdoses in 2020 was opioid-related, especially heroin-related, and we see an overall opioid-overdose increase of 39% from 2019 to 2020 (Gjersing, 2021).

Addiction is a prominent and lasting public health problem with somber statistics. This scoping review is therefore of great relevance to public health research, as the aim is to shed light on new possible ways of solving mental health problems, and more specifically substance dependence.

2.0 Background

2.1 Current treatment options

Statistically, addiction, particularly addiction to narcotics, seems to be a growing problem with a limited range of treatment options, especially for those who conventional pharmaceutical and behavioral interventions have little to no effect (Nigam & Pandurangi, 2021). There have been varying results from trials investigating different psychological and psychosocial interventions, most concluding the treatments as effective, but with room for improvement (De Crescenzo et al., 2018). Psychotherapy (PT), Mindfulness-Based Relapse Prevention (MBRP), Cognitive Behavioral Therapy (CBT), and Emotional Enhancement Therapy (MET) utilizes many of the same principles and are four acknowledged psychological and behavioral interventions for treating addiction and other mental health disorders (Leeman et al., 2014). Trials investigating psychological and psychosocial interventions mostly deduce the treatments as effective and promising, but with room for improvement, especially for long-term abstinence (De Crescenzo et al., 2018). This is also seen in studies investigating different pharmacological treatments for addiction, among them disulfiram, naltrexone, and acamprosate for alcoholism, and buprenorphine and methadone for opioid addiction (Ducharme et al., 2012; Liang & Olsen, 2014; Mattick et al., 2009). The treatments are considered more effective when in combination with behavioral platforms (Carroll et al., 2004), but are also associated with many unpleasant side effects (Ducharme et al., 2012; Liang & Olsen, 2014; Mattick et al., 2009).

There are also many combinational treatment models available. Trauma Interventions using Mindfulness-Based Extinction and Reconsolidation of memories (TIMBER) is a targeted mindfulness-based cognitive behavioral therapy that can be used both independently or in combination with pharmacological interventions or other treatment models like Repetitive Transcranial Magnetic Stimulation (rTMS) (Pradhan et al., 2019). rTMS is a noninvasive treatment method mostly used when treating patients with depressive disorder, utilizing magnetic fields to stimulate nerve cells in the brain and consequently improve any depressive symptoms (Janicak & Dokucu, 2015). Despite limited data on its application in addiction treatment, some preliminary evidence shows that rTMS treatment to the prefrontal cortex can reduce craving for patients with alcohol, cocaine, nicotine, or cannabis dependence (Pradhan & Rossi, 2020).

2.2 The pathophysiology of addiction

To better understand how psychedelics have role to play in addiction-treatment and how they affect us physically and mentally, we have to consider the pathophysiology of addiction. This is an intricate process that is still not well understood, involving the release and uptake of serotonergic and glutamatergic neurons in the brain`s reward circuit. More specifically, the release and uptake between the ventral tegmental area (VTA), the prefrontal cortex, and nucleus accumbens (NAc) (Kalivas & Volkow, 2005).

Drugs with abuse potential (such as cocaine, heroin, and alcohol) highjack the brain`s reward circuit and reinforces the harmful behavior that promotes drinking or doing drugs through a complicated process of learning by stimuli and seeking said stimuli for continued reward (Kalivas & Volkow, 2005). For a first-time user, the administration of drugs or alcohol will activate the serotonergic system and release a projection of dopamine from the VTA and throughout the reward circuit (MacNicol, 2017). This results in neuroplastic changes in the brain and learned associations that makes for a more effective initiation of the adaptive behavioral response the next time the user administers drugs or alcohol (Kalivas & Volkow, 2005). This learned association, also known as Maladaptive Reward Memories (MRM), takes part in encoding the brain`s learning process and subsequent behavior – harmful, drug-seeking behavior included (Das et al., 2019). The behavioral response to the stimuli will still be goal-oriented even after the behavior is well learned and the MRMs are formed. Continued dopamine-release is no longer necessary for the learning process but persists with continued exposure to the stimuli (Kalivas & Volkow, 2005).

Prolonged use and continued dopamine-release ultimately results in hyperactivity in the prefrontal cortex and cellular changes in glutamatergic projections from the prefrontal cortex to the NAc. Such changes in the plasticity (ability to change activity in response to stimuli) of the prefrontal cortex`s excitatory neuron-release (outgoing release of glutamate), in turn reduced the NAc`s ability to regulate its own neurotransmissions. It can no longer respond appropriately to biological rewards (such as drugs or alcohol) or control the drug- or alcohol-seeking behavior (Kalivas & Volkow, 2005). As the usage becomes habitual and the user goes from recreational user to addict, the effects from the drugs or alcohol decreases as craving and the drug-seeking behavior increases (MacNicol, 2017). Long-term exposure to stimuli has also been linked to reduced neuroplasticity, cognitive function, and ability to learn new behaviors (Rieser et al., 2021).

2.3 The pharmacology of psychedelics and their use in addiction-treatments

Classic hallucinogens such as lysergic acid diethylamide (LSD) and psilocybin, as well as the entactogenic psychedelic substance 3,4-methylenedioxymethamphetamine (MDMA), targets the serotonergic system in different ways (Bogenschutz & Johnson, 2016; Kolp et al., 2014; Sessa, 2019). The antagonist psychedelic substance ketamine hydrochloride (ketamine) targets the glutaminergic system. In this way the substances create a psychological landscape where the subject is susceptible to behavioral change, while receiving the emotional support needed to tackle sobriety (MacNicol, 2017). There is still much we don't know and understand about these mechanisms and how they affect the brain`s neuroplasticity, but existing research indicates great potential in addiction-treatment (Krebs & Johansen, 2012).

2.3.1. LSD and Psilocybin

Perhaps the most known amongst the classic psychedelic substances are LSD and psilocybin. Even though there`s limited research utilizing psilocybin in an addiction-related context, there`s extended research on LSD and its possible applicability in treating addiction disorders (Bogenschutz & Johnson, 2016). As mentioned, the classic psychedelic substances target the serotonergic system in different ways. What seems to be a recurrence for all is the mediating effect on the 5-hydroxytryptamine receptors 2A (5HT2A receptors), which are key components in modulating the serotonergic and glutaminergic systems (Bogenschutz & Johnson, 2016). Animal studies investigating these effects found that psychedelics increase neuritogenesis, spinogenesis, and synaptogenesis, three processes in which key components of the nervous system are developed. In addition to regulating the gene expression of several genes associated with neuroplasticity, which in turn is mediated by activating the 5HT2A receptors. This has yet to be confirmed in humans, but it is a possible hypothesis (Rieser et al., 2021).

If correct, the increased neuroplasticity should increase the addict`s ability to learn, adapt, and understand, and subsequently achieve behavioral change. In addition, activation of the 5HT2A receptors is associated with the release of serotonin (Bogenschutz & Johnson, 2016; Rieser et al., 2021). Serotonin is an important neuron when regulation stress, anxiety, cognitive function, and social behavior. This effect on the serotonergic system will in theory reduce stress and anxiety, which are triggers for craving and relapse, increase the addict's sense of belonging, empathy, and prosocial behavior, as well as give the confidence needed to

confront instead of avoiding negative emotions. Much of psychedelics positive effects have also been described to be a result of subjective experiences created by the hallucinogenic effects of the substances, so-called mystical-type experiences that gives the individual increased insight, interception, and self-awareness – all important tools in the recovery process (Rieser et al., 2021).

2.3.2. MDMA

As an entactogenic phenethylamine, MDMA is not technically a classic psychedelic, and is perhaps most known as a popular underground party drug under the street name "ecstasy". But in addition to having hallucinogenic effects at high doses, MDMA is also an indirect serotonin agonist (Sessa, 2019). This means association with activation of the 5HT2A receptors and release of serotonin, noradrenaline, and (in a much smaller scale) dopamine. It is also hypothesized that MDMA has a mediating effect on the release of oxytocin and reduces the fear-response in the amygdala (Perkins et al., 2021). As with the classic psychedelics, MDMA is associated with increased empathy, compassion, and a feeling of closeness and unity with others. Serotonin will also contribute to reduce depression, anxiety, and stress, which in turn will contribute to a positive mood and increased self-confidence. Dopamine and noradrenaline raise awareness and increases motivation, and together with reduces fear response makes MDMA the "perfect drug" for trauma-related disorders and avoidance behavior, as it lowers the barrier that makes confrontation of negative emotions less stressful and daunting (Sessa, 2019).

2.3.3. Ketamine

The phencyclidine derivative known as ketamine is also not technically a classic psychedelic and most known and used as an anesthesia, for instance as a general anesthesia during tapering of opioids (Kolp et al., 2014). But ketamine also has a direct and indirect effect on the serotonergic and dopaminergic systems, and its primary targets are the excitatory messenger neurotransmitters glutamate (Nigam & Pandurangi, 2021). Its effect on the glutaminergic system is the most interesting aspect, as ketamine works as an antagonist for the N-methyl-D-aspartate (NMDA) receptors, subsequently blocking glutamate activation in the brain (Kolp et al., 2014). When activated, these NMDA receptors ultimately reorganize and reconsolidate MRMs after destabilization, reinforcing their effect. Research indicates that the antagonist can delay this process and prolong the "reconsolidation window" for administration of different behavioral treatments while the patient is susceptible to change –

so-called MRM retrieval (Das et al., 2019; Kolp et al., 2014). Extensive research has also been conducted investigating the antidepressant effect of ketamine, which started out as unexpected outcomes in studies with different intentions. Nevertheless, these antidepressant effect seem to be transient and the mechanism behind are still unclear. Much of this effect was previously explained by the compounds hallucinogenic and dissociative properties, as something mystical and subjective related to the so-called afterglow effect. There is increasing disagreement around this in recent years, which in turn have sparked interest for even more research into the compound's possible properties (Kolp et al., 2014).

2.3.4. But are psychedelic substances addictive?

Questions are rising about psychedelics' addictive potential and whether these treatments could lead to replacing one addiction with another. Nutt et al. (2010) performed a multicriteria decision analysis (MCDA) with members of the Independent Scientific Committee on Drugs and two independent specialists, to establish scores for 20 representative drugs and their addictive potential. Out of the 20 included drugs, psilocybin, LSD and MDMA had some of the lowest scores with 6, 7 and 9, respectively. Ketamine scored 15, while alcohol (score 72) and heroin (score 55) were at the top with the highest scores (Nutt et al., 2010).

There has been some debate about ketamine`s addictive potential, as the substance was described to have a significant potential for dependence in the early 2010s. This was at a time where the substance was more frequently used as a recreational drug with other more known "party drugs" like MDMA, often in combination with other drugs or alcohol. Still there seems to be enough research confirming that administration during clinical trials under strict supervision does not increase the risk of developing dependence significantly (Kolp et al., 2014). Overall, this would not indicate a high risk of dependency, at least not compared to alcohol or opioids.

2.4 History and context of therapeutic psychedelic-assisted treatments

The first psychedelic-assisted trial was conducted by Werner Stoll in 1947 at the University of Zurich, administering LSD to 6 patients with treatment-resistant schizophrenia, as referenced by Nichols and Walter (2021). The trial showed thought-provoking results, but it was noted in Werner Stoll`s summary in 1949 of the then two existing clinical reports, that the desired therapeutic effects (as observed in the control groups) did not occur in patients with

schizophrenia (Nichols & Walter, 2021). Still, when Sandoz Pharmaceuticals made LSD-25 available for research institutes and physicians with the trade name "Delysid", it led to several trials investigating the effect of different psychedelics on patients with a range of psychiatric disorders (addiction, obsessive-compulsive disorder, depression, schizophrenia), as well as emotional problems in veterans (Nichols & Walter, 2021). The University of Saskatoon, Saskatchewan, almost exclusively offered alcohol treatments with LSD from 1953. The many reports published in the seven years they were operational, showed that LSD-assisted therapy for alcoholism was either beneficial, or at least very promising (Nichols & Walter, 2021). Numerous studies were conducted in the next decade, to which some are included in a meta-analysis of randomized control trials to evaluate the clinical effect of LSD in the treatment of alcoholism, performed by Krebs and Johansen (2012). Based on only six eligible trials with 536 participants, they found evidence of a beneficial effect of LSD on alcohol addiction. They concluded their research by stating that just a single dose of LSD, thought constricted to a rehabilitating treatment context, was associated with a reduction in alcohol consumption and abuse (Krebs & Johansen, 2012).

As psychedelics were attracting attention due to its increasing use in clinical trials for different mental health disorders, there was also a rise in recreational use in the 1950s and 60s (Bogenschutz & Johnson, 2016). As a result of this and increasing political unrest, all clinical research on psychedelics were stopped with the enactment of the Controlled Substances Act in 1962 (Nichols & Walter, 2021). All such substances (except for ketamine) were classified as Schedule I drugs, highly restricted compounds (Bogenschutz & Johnson, 2016). Ketamine was later in 1999 placed as a Schedule III drug (Kolp et al., 2014).

2.4.1 Promising results from animal studies

When the last ongoing study ended in 1976, there were no more clinical trials on psychedelics until 1994 – but Strassman`s study on intravenous N,N-Dimethyltryptamine (DMT) did not focus on therapy (Strassman et al., 1994). Still, multiple experiments using animal models in the coming decades were conducted, which made a link between psychedelics effect on the serotonergic and glutaminergic systems and addiction (Nichols & Walter, 2021). Vaidya et al. (1997) and associates identified a link between the expression of a specific gene responsible for increased neuroplasticity and activation of the $5HT_{2A/2C}$ receptors. This gene was observed to be downregulated by stress, but this downregulation seemed to be blocked by the activation of the 5HT receptors, subsequently increasing the brain`s neuroplasticity and ability for behavioral change (Vaidya et al., 1997).

In 2011, Katsidoni and affiliates wrote an article where they successfully identified the neural substrates involved in the reward-facilitating effect of cocaine in rats, as well as modulation of this through the 5HT receptors in the prefrontal cortex and the nucleus accumbens (Katsidoni et al., 2011). Another interesting connection was made by Alper et al. (2018), who found that just a single dose of LSD in mice significantly reduced ethanol consumption or preference. Later, the introduction of Magnetic Resonance Imaging (MRI) and Single photon-emission computed tomography (SPECT) made it possible to map and observe the brain while under the influence of psychedelics and identify changes in mood and perception, as well as key component of the brain in addiction research (Nichols & Walter, 2021).

2.4.2 Lack of comparable research practices and guidelines

In addition to psychedelics being a new and exciting (but potentially dangerous) substance at the time, there were no regulations and limited access to guidelines for research into psychedelics for psychiatry. Several meta-analysis and reviews performed after the "psychedelic shut-down" in the 60s, have commented on methodological limitations regarding inconsistently defined treatment groups and application of treatment among groups, lack of control groups, blinding, and follow-up, adverse events and outcomes were often not reported, and statistical analysis and power calculations were often omitted (Rucker et al., 2018).

Krebs and Johansen (2012) included only six studies in their meta-analysis investigating LSD in alcohol dependency-treatments. Most trials were excluded based on being non-randomized, quasi-randomized, open label or case reports – as well as duplicates or articles of no relevance. Belouin and Henningfield (2018) voiced in their commentary several areas of concern for future research, including when and how these substances should be used, and how to evaluate who is eligible to participate in the treatments. Subsequently, there seems to be some evidence of concern regarding the safety of the patients and therapists participating in previously conducted treatments. After an evaluation of the conduct of psychedelic therapy at Modum Bad Nervesanatorium, Norway, from 1961 to 1976, Johnstad (2020) reported two (alleged) cases where the participants experienced so-called "bad-trips" caused by the doctors "non-conformity with good practice guidelines".

These flaws have been addressed by many post-prohibition research strategies, introducing strategies (Rucker et al., 2018), checklists (Petranker et al., 2020), and safety guidelines (Johnson et al., 2008) for conducting psychedelic research. These ensure the safety of all

participants, transparency, and provide grounds for comparison and extension of the research. Hopefully, by using guidance and principles from these articles, it should provide a higher scientific standard with research that is rigorous and transparent (Petranker et al., 2020).

2.5 A new era of psychedelic research

Due to promising results in both animal- and human studies, it is now possible to use some of the previously class 1 scheduled drugs in medical research, among them ketamine (received Food and Drug Administration (FDA) approval, legally available with prescription), psilocybin (received "breakthrough therapy" status by the FDA for treatment of alcohol use disorder, major depressive disorder and treatment-resistant depression) and MDMA (received "breakthrough therapy" status by the FDA) (Nigam & Pandurangi, 2021). MDMA are now undergoing phase 3 of clinical trials for treating PTSD in the US, Canada, and Israel, while countries like Norway, Czech Republic and Germany are still undergoing phase 2 trials (*MAPS source*). Ketamine has to some extent been used from 1975 (Kolp et al., 2014), but most of the research connected to addiction and addiction treatments were published from 1992, starting with the early research of the Russian researcher, Evgeny Krupitsky (Krupitsky et al., 2002; Krupitsky et al., 2007; Krupitsky et al., 1992; Krupitsky & Grinenko, 1997).

Subsequently, we have seen great progress in the field since the reinitiation of psychedelic research in the 90s (Barnett et al., 2022). However, to my knowledge, there is limited psychedelic research performed in Norway since the reinitiation – despite what looks like increased interest among the Norwegian population (and so-called "psychonauts") and scientists from many different professions. This bloom of awareness is evident on platforms like Facebook, Twitter, and Reddit, where like-minded individuals meet and share knowledge and experiences (e.g., the Facebook pages "Norsk Psykedelisk Forum" and "Studentenes Forening for Psykedelisk Vitenskap") (Norsk Psykedelisk Forum, n.d.; Studentenes Forening for Psykedelisk Vitenskap, n.d.).

2.5.1 Psychedelic-assisted therapy in Norway

The only study performed in Norway identified though databases in a preliminary search was the LSD-assisted treatments at Modum Bad Nervesanatorium from 1961-1976 (Madsen & Hoffart, 1996), strongly criticized by Johnstad (2020) in his evaluation of the treatments. This study included patients with alcoholism, drug addiction, psychoses, obsessive neuroses, other psychoneuroses, sexual deviation, and other disorders of character (Madsen & Hoffart, 1996).

Three studies performed in Norway were identified through public trial registries (*source*). COMPASS Pathways Ltd sponsored a psilocybin-assisted trial for patients with *treatment-resistant depression* (TRD), completed in 2019 (COMPASS Pathways Ltd, 2018, May 31 - 2019, August 31). The *Multidisciplinary Association for Psychedelic Studies* (MAPS) are behind the other two studies, both ongoing and utilizing MDMA, one treating *major depressive disorder* (MDD) (Østfold Hospital Trust, 2021) and the other PTSD (MAPS, 2022).

2.6 Problem statement

To my knowledge, there are no studies focusing on the use of psychedelics in treating alcoholism or drug addiction in Norway, except for the questionable treatment programs at Modum Bad Nervesanatorium (Madsen & Hoffart, 1996). There does however seem to be some openness and curiosity to the concept based on the few ongoing studies concerning depression and PTSD, presenting an opportunity for a scoping review. With addiction being such a lasting and prominent issue in the Norwegian population, and the current treatment options being somewhat limited, there is a wish to explore the use of psychedelics in addiction-treatment and introduce this concept in Norway. In doing so, this scoping review will synthesize the available evidence on selected psychedelic substances used for treating addiction to alcohol and other illicit substances. The aim is to present an overview of relevant studies performed after the reinitiation in the 90s, which will cast a light on the current situation internationally. The scoping review will identify and chart knowledge gaps, limitations with previously conducted research and present potential strategies to inform research of psychedelics in Norway.

3.0 Method

The Joanna Briggs Institute (JBI) Manual for Evidence Synthesis for methodological guidance was utilized in this scoping review (Aromataris & Munn, 2020). The aim was to create an overview of available evidence on the pre-selected psychedelic substances used in addiction treatment for alcohol and narcotic substances, as well as identify knowledge gaps and limitations with previously conducted research.

A preliminary literature search in the databases Ovid Medline, Scopus, and Web of Science indicated little research with psychedelics in Norway, and close to nothing relevant to alcoholism or drug addiction. To some extent, this can be explained by the substances being restricted by law, and that different substances are at different stages of clinical trials in psychotherapy (Kolp et al., 2014; Perkins et al., 2021). Despite these restrictions, the preliminary search uncovered a few studies researching psychedelics after the reinitiation in the 90s, indicating that psychedelic research might be a growing research field that also can be extended to Norway. This assumption offers an opportunity to synthesize the available research and use this to present potential strategies for continued research into psychedelic-assisted addiction treatments in Norway. A scoping review was therefore suitable for this kind of research question.

As a precaution in case the literature search did not give adequate information to conduct a scoping review, the researchers in charge of the ongoing project at Sykehuset Østfold HF, Norway, would be contacted to request the permission to perform expert interviews. This would provide primary information about the trial`s progress, prognosis, and the plan after trial completion (MAPS, 2022). The trial investigates MDMA as a tool in psychotherapy for patients with PTSD, which means the study is not eligible for inclusion for this review, but the information could potentially be used to explore the situation in Norway more in detail. However, after reconsideration of relevant contexts for inclusion, this was not necessary as there was enough available evidence to perform a scoping review without additional expert interviews.

3.1 Review questions

"An investigation of the research utilizing selected psychedelic substances in the treatment of addiction to alcohol or other drugs, since the reinitiation of psychedelic research in the 90s."

i. Since the reinitiation in the 90s, which substance addictions have been under investigation for treatment with psychedelic substances? What behavioral outcome measures or therapeutic gains were measured?
ii. Which psychedelic substances have been used in psychotherapeutic treatment research for addiction? Which dosage was prescribed?
iii. How was the psychedelic-assisted treatment applied? Were there any specific guidelines or treatment plans followed?

3.2 Inclusion criteria

3.2.1 Concept

This review included all studies researching the preselected psychedelic substances for treating addiction to alcohol or drugs in a therapeutic or clinical context, with relevance to therapeutic addiction treatment, a behavioral outcome, or therapeutic gain.

3.2.2 Participants

The population considered for this scoping review was limited to people with an alcohol or drug addiction, undergoing treatment with the included psychedelic substances. This included participants seeking treatment for their addiction, as well as those not motivated for treatment.

3.2.3 Context

All contexts using the included psychedelic substances in a therapeutic setting were considered eligible for inclusion. After conducting the comprehensive search, the decision to include contexts using psychedelics in a clinical setting were made, provided they had relevance to therapeutic treatment of addiction with a behavioral outcome or therapeutic gain.

3.2.4 Types of sources

Due to the nature of this scoping review, no restrictions were placed on the type of evidence collected. All study designs were to be included. However, reviews, meta-analysis, opinion papers, and letters were excluded if they did not present a full description of the treatments.

3.2.5 Eligibility criteria

Table 1: Eligibility criteria for inclusion and exclusion.

Inclusion	Exclusion
LSD, MDMA, psilocybin and ketamine.	Research into other mental health disorders, such as depression or schizophrenia.
Research period: since reinitiation of psychedelic research in the 90s (starting with the research published in Russia from 1992 (Krupitsky et al. 1992)).	Reviews, summaries, meta-analysis, opinion papers, letters, or symposiums.
Addiction treatment for alcohol or drug abuse with an outcome relevant to behavior, therapy, and addiction.	Studies about other addictions, such as addiction to tobacco or internet addiction.
Human participation in the trials.	Studies without a clear treatment plan and documentation.
Publications in the following languages: English, Norwegian, Swedish, and Danish.	

3.3 Search strategy

The search strategy was inspired by the JBI Guidance for conduction scoping reviews (Peters et al., 2020). Initial knowledge on the subject and keywords sourced from articles identified in the preliminary searches were used to build a comprehensive search that was executed in the following databases: *Ovid Medline, Embase (Ovid), APA PsycInfo, Scopus,* and *Web of Science*. The search strategy is divided into eight concepts containing keywords and synonyms for each (MDMA, LSD, psilocybin, ketamine, classification, problem, and intervention). Keywords collected for the final search process is presented in Appendix 1, and the first proposed search strategy is presented in Appendix 2. These were used when constructing the search strategy for the first comprehensive search executed January 29th. Following the search, all literature was uploaded to Endnote 20 (Clarivate Analytics, PA, USA), and duplicates removed. Because I was expecting numerous results, the titles were screened first to exclude non-eligible studies, before screening the abstracts. The presented inclusion criteria in Table 1 were used for this screening process. The included studies were limited to those performed after the reinitiation of psychedelic research in the 90s. The included studies were read full-text and assessed in detail against the inclusion criteria. Uncertainties about any studies were discussed with my supervisor. Lastly, a screening of reviews and references from the included studies was performed to identify additional studies missed by the database searches.

The initial final search did not give the desired amount of data to conduct the scoping review, so an additional comprehensive search was executed in agreement with my supervisor. A small change was done to a Boolean operator between concepts “substances” and

"classification", from "AND" to "OR", in the hopes of identifying significantly more data for screening. See Table 2 below for the final search strategy with the last changes, executed February 11th. All resulting literature were downloaded to EndNote 20 in a separate library, before it was merged with the previous library for the first comprehensive search for further screening.

The following registers, databases, or search engines were used to identify additional studies: REK-database (REK, n.d.), MAPS-register (MAPS, n.d.), Clinicalgovtrials.gov (U.S. National Library of Medicine, n.d.), and Research Gate (ResearchGate, n.d.). The studies identified in these databases were only included if the research had been published and presented with a clear treatment plan and results, as well as within the inclusion criteria.

Table 2: Search strategy for the final, comprehensive search executed February 11th. The table includes the used keywords and MeSH-terms for the seven concepts that were created during the preliminary search process. The Boolean operators "OR" and "AND" were utilized to direct the search.

Concept	Controlled vocabulary (MeSH)	Free keywords
Substance #1: MDMA	N-Methyl-3,4-methylenedioxyamphetamine/	("N-Methyl-3,4-methylenedioxyamphetamine" OR "3,4-methylenedioxymethamphetamine" OR mdma OR ecstasy OR xtc OR e)
Substance #2: LSD	Lysergic acid diethylamide/	("lysergic acid diethylamide" OR lsd OR lsd-25 OR acid)
Substance #3: Psilocybin	Psilocybin/	(psilocybin* OR "psilocybin mushroom*" OR "psychedelic mushroom*" OR "magic mushroom*" OR shroom*)
Substance #4: Ketamine	Ketamine/	(ketamine* OR ket OR k OR "ketamine hydrochloride*" OR calypsol OR "2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone")
#5: #1 OR #2 OR #3 OR #4		
#6: Classification	exp Hallucinogens/	(hallucinogen* OR Psychotropic* OR "psychedelic substance*" OR psychedelic* OR psychoactive* OR entactogen* OR empathogen*)
#7: Problem	Substance-related disorders/ OR exp Alcohol-related disorders/ OR Alcoholism/ OR exp Narcotic-related disorders/ OR exp Amphetamine-related disorders/ OR exp Cocaine-related disorders/	(alcohol* OR "alcohol related disorder*" OR "substance related disorder*" OR "Narcotic related disorder*" OR addict* OR "substance abuse" OR "drug abuse" OR "substance depend*" OR "drug depend*")
#8: Intervention	Psychotherapy/	(psychotherap* OR "psychedelic assisted psychotherap*" OR "substance assisted psychotherap*" OR "psychiatric treatment*" OR "psychosocial intervention*" OR "cognitive behavioral therap*" OR "psychedelic assisted therap*" OR "mdma assisted therap*" OR "psilocybin assisted therap*" OR psychopharmacotherap*)
#9: #5 OR #6		
#10: #9 AND #7 AND #8		

3.4 Study selection

Due to the interdisciplinary nature of the topic and the relatively recent emergence of psychedelics in psychotherapy, a broader approach was preferred over a systematic quality assessment. The aim of this review was to map the literature to see what has been done, not to evaluate the quality of the included studies or to measure a specific health outcome after an intervention, as is usual with systematic reviews. In that sense, scoping reviews are particularly useful since they bring together literature from diverse disciplines, and with different approaches to health, intervention, and measurement outcomes.

Some restrictions were put on the search, however, to make sure the material was within the scope of the reviews purpose. Studies were therefor excluded for not having a clear behavioral or psychological outcome related to the reviews purpose, for treating other addiction disorders (e.g., tobacco or internet addiction) or other mental health disorders (such as major depressive disorder or post-traumatic stress disorder), not having a clear treatment procedure with results, or focusing on self-medicating with psychedelic in a recreational context, among other things (defined by the inclusion criteria in Table 1).

Studies mainly treating withdrawal symptoms after substance tapering under ketamine general anesthesia were excluded (Wong et al., 2015), as these only presented clinical outcomes (number of days in the intensive care unit (ICU), need for intubation, vital signs, need for additional benzodiazepines during tapering, etc.) with no relevance to therapy or the purpose of this review. Since the review is linked to mental health and addiction, the original plan was to only include studies with relevance to therapy that utilize some form of therapeutic practice in their treatment. But as several relevant studies with a clear behavioral outcome or therapeutic gain were excluded based on this, the choice to also include studies in a clinical setting was made, which opened screening of several studies.

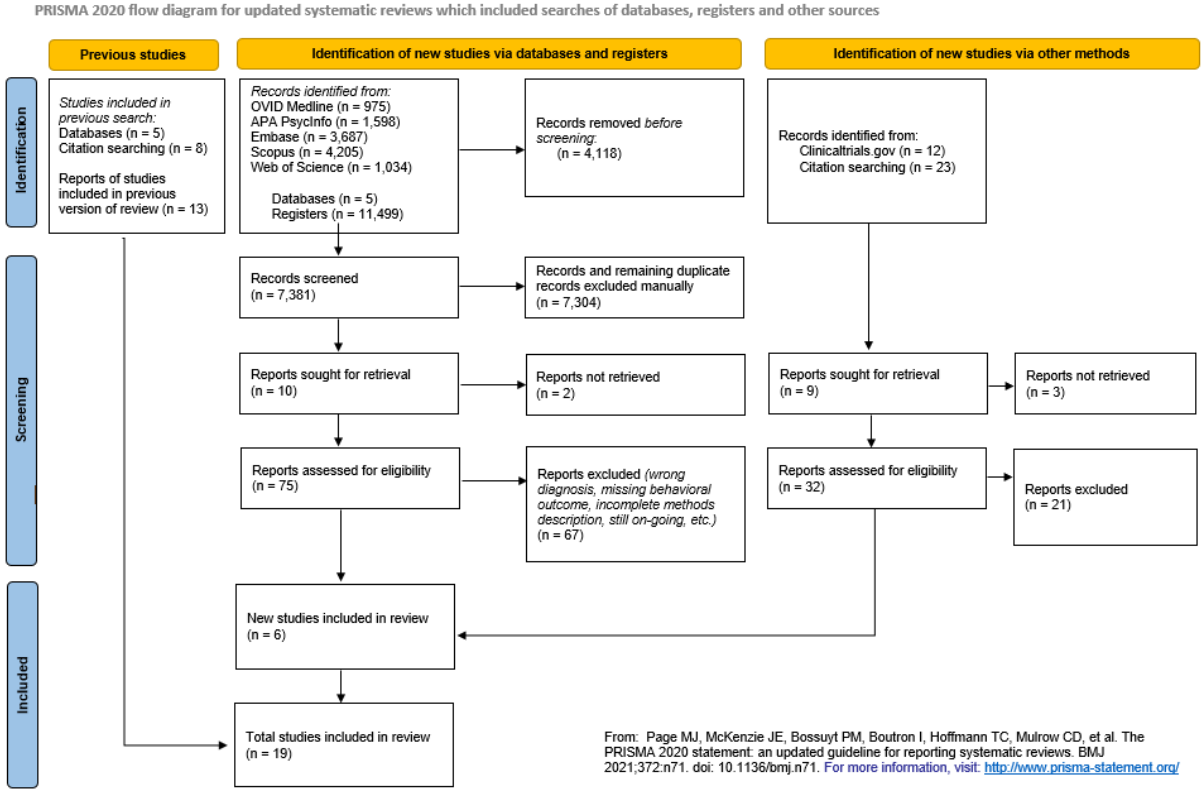
The initial thought, upon deciding which psychedelic substances to include for this review, was to only include classic psychedelics (LSD, DMT, mescaline, and psilocybin) with similar pharmacology (Rucker et al., 2018). Mescaline, found in the Peyote or San Pedro cactus, ibogaine derived from the bark of the iboga shrub, and the Amazonian tea ayahuasca (Rucker et al., 2018) were excluded, as these compounds were (seemingly) used in spiritual rituals for the most part without clear treatment procedures. Preliminary searches indicated little research with DMT, so this was also excluded. Even though MDMA is not technically a classic psychedelic substance, it was envisioned included from the beginning because of its use in recent clinical trials in Norway. Lastly, ketamine was originally not included, but was added as amounting research was identified during the preliminary search, indicating its importance.

3.5 Data charting and presentation

The search decision process is presented as a flowchart in figure 1, inspired by the PRISMA 2020 flow diagram (Page et al., 2021), including search results from selected databases, removed duplicates, successful retrievals, and additional studies found through citation searching or other additional sources. It also includes the identified studies from the first comprehensive search January 29th, presented on the left side of the figure.

A self-made data charting tool was used on all the included studies to retrieve the information deemed relevant by the inclusion criteria; a process called data charting. This procedure and the a priori data charting tool were pilot tested to make sure all relevant data was included for the analysis and to avoid misinterpretations. The a priori data charting tool is presented in Appendix 3. A few changes were made based on the pilot test using articles from this reviews data collection. “First author (year)” was changed to “group” and “treatment/intervention” was changed to “timeline for treatment/intervention”. “Practice guidelines” and “study protocol” was removed due to low reporting of guidelines and protocols in the included studies, while “trial identification”, “diagnosis (with diagnostic criteria”, “concomitant drug use”, “psychiatric comorbidities”, “purpose”, “pre-registration (analysis plan and/or study protocol”, “study measures”, and “additional relevant information” were added. Under “population”, gender distribution “male/female” and “age” were added. The final data charter tool with the gathered information from all the included studies are presented in Appendix 4. The data gathered with the data charter tool was then synthesized and presented in relevant tables to make it possible to map and compare the included studies, and to systematically divide and visualize the data. The chartered results prepared in tables can be found under results.

Figure 1: Search decision from the final comprehensive search presented as a flowchart, inspired by the PRISMA 2020 flow diagram (Page et al., 2021). Updated version including reports from previous search (January 29th) and the last search (February 11th).



Note. From: Page M. J., McKenzie J. F., et al. (2020). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. Doi: 10.1136/bmj.n71.

4.0 Results

A first comprehensive search identified 13 studies, which was deemed too few to make any recommendations to inform the research to Norway. To achieve a broader scope of the field, the search strategy was revised and adapted to include studies in a clinical setting, investigating a therapeutic treatment of addiction and presenting behavioral or psychological outcomes. This was especially aimed at including studies investigating opioid tapering with ketamine as general anesthesia, as it had been noted during the search performed January 29th that at least two studies like this had been excluded.

Through this additional search, another six studies were identified for inclusion, completing the search decision process with 19 included studies for this review.

Underneath, the data presentation will start with a general study description of the included studies, with addiction type, study design, location, study period, and participant demographics. Following, the treatment methods with selected psychedelic substance (and control substance/intervention if applied), and treatment context are presented. Finally, treatment outcomes relevant to this review's purpose (abstinence and craving, mindfulness and spirituality, depression, and anxiety) will be summarized.

4.1 General study description

The study characteristics are presented in Table 3. Of the 19 included studies, eight investigated alcohol abuse (study # 1-8), three cocaine abuse (study # 9-11), six opioid abuse (including heroin and prescription opioids) (study # 12-17), one cannabis (Azhari et al., 2021), and one polysubstance abuse (stimulants, cannabis, and classic psychedelics) (Johnson & Black, 2020).

Most studies were conducted in the United States (US) (study # 1-2, 5, 9-11, and 16-18) or Russia (study #6-7 and #13-14), the latter utilized ketamine for different addictions under the supervision of one researcher, Evgeny Krupitsky MD, PHD. Another recurring researcher is Elias Dakwar MD, who either was the lead investigator or a co-author for the majority of the trials executed in the US (study #2 and 9-11) .

As seen in Table 3, study dates were not reported in six trials (study # 6-7, 13-14, and 16-17), with the remaining studies being performed between 1996 and 2020, and the majority performed after 2010.

One study with 70 participants (Kolp et al., 2006) and one with three participants (Pradhan & Rossi, 2020) did not report gender distribution. Among the 920 participants in the 17 remaining studies, 758 (82.4%) were men and 162 (17.6%) women, with a wide age range. Study design distribution comprised of one empirical observational study (Kolp et al., 2006), three case reports(study # 15-16 and 19), four proof of concept studies (study # 1, 8, and 17-18), and 11 clinical trials at different stages (study # 2-4, 6-7, and 9-14).

Table 3: General study description including addiction-type, study design, location, study period, transparency, and number of participants.

#	Group	Addiction	Study design	Study location	Study period	Pre-registration, open data and open materials	Participants, n
1	Bogenschutz et al. 2015	**Alcohol**	Open label, proof of concept study	Albuquerque, USA	2012 – 2014	No	10
2	Dakwar et al. 2020	**Alcohol**	Triple-blind, randomized controlled pilot trial	New York, USA	2014 – 2017	Yes	40
3	Das et al. 2019	**Alcohol**	Single-blind, randomized controlled trial	London, UK	2015 – 2018	No	90
4	Grabski et al. 2022	**Alcohol**	Double-blind, randomized controlled phase II trial	London, UK	2016 – 2020	Yes	96
5	Kolp et al. 2006	**Alcohol**	Empirical clinical observations	USA	1996 – 1999	No	70
6	Krupitsky and Grinenko 1997	**Alcohol**	Non-randomized clinical trial	St. Petersburg, Russia	Not reported	No	211
7	Krupitsky et al. 1992	**Alcohol**	Randomized clinical trial	Russia	Not reported	No	186
8	Sessa et al. 2021	**Alcohol**	Open label, proof of concept feasibility study	Bristol, UK	2018 – 2020	No	14
9	Dakwar et al. 2014	**Cocaine**	Triple-blind, randomized controlled crossover trial	New York, USA	2011 – 2012	No	8
10	Dakwar et al. 2017	**Cocaine**	Double-blind, randomized controlled crossover trial	New York, USA	2013 – 2015	No	20
11	Dakwar et al. 2019	**Cocaine**	Randomized controlled trial	New York, USA	2011 – 2016	No	55
12	Jovaisa et al. 2006	**Opioids**	Double-blind, randomized controlled trial	Vilnius, Lithuania	2003 – 2006	No	50
13	Krupitsky et al. 2002	**Heroin**	Double-blind, randomized controlled trial	St. Petersburg, Russia	Not reported	No	70
14	Krupitsky et al. 2007	**Heroin**	Double-blind, randomized trial	St. Petersburg, Russia	Not reported	No	59
15	Lalanne et al. 2016	**Opioids**	Case report	Strasbourg, France	2015	No	1
16	Ocker et al. 2020	**Opioids**	Case report	Philadelphia, USA	Not reported	No	1

17	Pradhan and Rossi 2020	**Opioids**	Open-label, proof of concept study	Camden, USA	Not reported	No	3
18	Azhari et al. 2021	**Cannabis**	Single-blind, uncontrolled proof of concept trial	New York, USA	2016 – 2018	Study protocol, not analysis plan	8
19	Johnson and Black 2020	**Stimulants and cannabis**	Case report	Australia	2015 – 2019	No	1

4.2 Participant characteristics

Table 4 summarizes participant characteristics to highlight psychiatric comorbidities, medication, or other characteristics that potentially could affect the treatments, or make a comparison of the outcomes difficult.

Of the included studies, four (study # 3, 6-7, and 16) did not report a formal diagnosis, and four (study # 6-7, and 16-17) did not report using a specific form of diagnostic criteria for their participants, such as the Diagnostic and Statistical Manual of Mental Disorders (DMS), International Classification of Diseases and (ICD), Alcohol Use Disorders Identification Test (AUDIT), or urine toxicology screening. The participants who have not undergone a complete screening and has received a diagnosis using concrete diagnostic criteria, might have different levels of alcohol or drug consumption, in addition to difference in motivation.

One study with 70 participants (Kolp et al., 2006) and one with three participants (Pradhan & Rossi, 2020) did not report gender distribution. Among the 920 participants in the 17 remaining studies, 758 (82.4%) were men and 162 (17.6%) women, with a wide age range.

Concomitant drug use were not reported in the Krupitsky and Grinenko (1997), Ocker et al. (2020), and Pradhan and Rossi (2020) studies. It was however reported in four studies (study # 4-5, 8, and 15), whereas one of them, the (Kolp et al., 2006) study, also stated that some of their participants had additional addictions and a range of different medicated mental disorders, without providing a complete dataset with participant characteristics. Any additional medication or use of drugs during the treatments has the possibility to affect the treatments and the psychedelic experience in unpredictable ways, so it is possible that some outcomes could be affected by this. The 13 remaining studies did not include participants with concomitant drug use (study # 1-3, 9-14, 16, and 18-19).

Psychiatric comorbidities varied among the included studies. There was no mention of any psychiatric comorbidities in the Krupitsky et al. (1992), Ocker et al. (2020), and Pradhan and Rossi (2020), so it is unclear what kind of mental state these participants were in and whether there was any contraindicated disorders or medication. Out of the remaining 16 studies, four

reported additional psychiatric disorders among their participants (study # 4, 8, 15 and 19). In one of these studies, the Grabski et al. (2022), it was noted that their participants did not have any psychiatric comorbidities except for depression and anxiety, while it in the Sessa et al. (2021) study was reported that most of the patients had psychiatric comorbidities, and this was mainly depression and anxiety. Since addiction, depression and anxiety often go hand in hand and there seem to be some disagreement among the researcher on what should be included as psychiatric comorbidities, it is possible that participants in the studies without reports of this, might in fact have depression and/or anxiety, or even other additional disorders who have not been stated.

Table 4: Participant diagnosis, diagnostic criteria, age and gender distribution, concomitant drug use, and psychiatric comorbidities.

#	Group	Diagnosis	Diagnostic criteria	Age	Gender distribution (male/female)	Concomitant drug use (yes/no)	Psychiatric comorbidities (yes/no)
1	Bogenschutz et al. 2015	AUD	DSM-IV for AUD	25-56	6/4	No	No
2	Dakwar et al. 2020	AUD	DSM-IV for AUD	Mean age 53.0±9.8	19/21	No	No
3	Das et al. 2019	High drinking levels	AUDIT scores 22.13±4.93	Mean age 27.48±8.11	55/35	No	No
4	Grabski et al. 2022	AUD	DSM-IV for AUD	Mean age 44.1±10.6	61/35	Yes	Yes
5	Kolp et al. 2006	AUD	DSM-IV for AUD	21-64	Not reported	Yes	No
6	Krupitsky and Grinenko 1997	Treatment-resistant, unable to maintain sobriety for a 3-month period, and several years of alcohol withdrawal symptoms	Not reported	Mean age 36.5±7 (active) and 38.4±0.81 (control)	211/0	Not reported	No
7	Krupitsky et al. 1992	Treatment-resistant, unable to maintain sobriety for a 3-month period, experienced withdrawal symptoms	Not reported	Mean age 33.4±1.07 (active) and 38.4±0.47 (control)	186/0	Not reported	Not reported
8	Sessa et al. 2021	AUD	DSM-IV for AUD	18-65	8/6	Yes	Yes
9	Dakwar et al. 2014	OUD	DSM-IV for OUD	Mean age 47.5±5.5	7/1	No	No
10	Dakwar et al. 2017	SUD	Active dependence with at least 8 days of use or 4 binges of large	Mean age 48.6±6.1	11/9	No	No

			amounts over the past 30 days, and at least one positive utox during screening				
11	Dakwar et al. 2019	SUD	DSM-IV for SUD	Mean age 47.0±9.3	41/14	No	No
12	Jovaisa et al. 2006	OUD	DSM-IV or ICD-10 for OUD	Mean age 22.7±3.0 (active) and 23.4±3.1 (control)	43/7	No	No
13	Krupitsky et al. 2002	OUD	DSM-IV or ICD-10 for OUD	Mean age 23.0±4.4 (active) and 21.6±3.0 (control)	55/15	No	No
14	Krupitsky et al. 2007	OUD	DSM-IV or ICD-10 for OUD	18-35	49/10	No	No
15	Lalanne et al. 2016	Opioid-induced hyperalgesia and chronic lumbar pain	DSM-IV for OUD	36	0/1	Yes	Yes
16	Ocker et al. 2020	Opioid-induced hyperalgesia and CRPS-I	Not reported	55	1/0	No	Not reported
17	Pradhan and Rossi 2020	OUD	Not reported	Not reported	Not reported	Not reported	Not reported
18	Azhari et al. 2021	CUD	DSM-IV for CUD	Mean age 42.5±13.5	4/4	No	No
19	Johnson and Black 2020	SUD, CUD	DSM-IV for SUD, CUD and MDD	22	1/0	No	Yes

Note. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition; AUD: Alcohol use disorder; AUDIT: Alcohol use disorder identification test; OUD: Opioid use disorder; SUD: Stimulant use disorder; ICD-10: International Classification of Diseases 10th edition; CRPS-I: Complex regional pain syndrome type 1; CUD: Cannabis use disorder; MDD: Major depressive disorder.

4.3 Treatment models and objectives

Table 5 summarizes the different combinations of treatment interventions and tools used in the included studies for treating the different addictions. The table consists of main purpose, psychedelic substance, placebo substance/control intervention, treatment context, and follow-up length.

Among the 19 identified studies, one utilized MDMA (Sessa et al. 2021), one LSD (Johnson and Black, 2020), one psilocybin (Bogenschutz et al. 2015), and 16 used ketamine (ref. Table 5). Eight studies were uncontrolled, while the remaining 11 used different pharmacological and/or therapeutic control methods.

Two studies did not use any form of therapy, mindfulness exercises, counseling, education, or rehabilitation prior to, during, or after the psychedelic treatments (Dakwar et al., 2017; Lalanne et al., 2016). Both Dakwar et al. (2016) and Lalanne et al. (2016) demonstrated how ketamine-assisted addiction treatments produced successful outcomes related to abstinence, without utilizing any behavioral interventions. Dakwar et al. (2017) treated 20 cocaine addicts using the verbal choice procedure for self-administration of cocaine in combination with intravenous ketamine to detect any changes in the relative salience of cocaine now vs. money later. Lalanne et al. (2016) used gradual opioid tapering under ketamine general anesthesia to reduce ay pain that might arise, and minimize withdrawal symptoms (e.g., craving), in a patient presented with chronic pain and dependence to prescription opioids.

The remaining studies utilized some sort of therapeutic practice in their treatment models, either alone or in combination with other treatments. Nine studies used psychotherapy (ref. Table 5), one cognitive behavioral therapy (Ocker et al., 2020), three motivational enhancement therapy (Azhari et al., 2021; Bogenschutz et al., 2015; Dakwar et al., 2020), three mindfulness-based relapse prevention (Azhari et al., 2021; Dakwar et al., 2019; Grabski et al., 2022), one alcohol education (Grabski et al., 2022), and one addiction counseling (Krupitsky et al., 2007). One study offered mandatory aftercare programs, either abstinence-based, outpatient counseling, or residential rehabilitation programs (Jovaisa et al., 2006), one used TIMBER in combination with rTMS (Pradhan & Rossi, 2020), and one study used relaxation and mindfulness exercises in combination with aversion therapy (Krupitsky & Grinenko, 1997)

Some studies used combinations of the methods mentioned above, e.g., motivational enhancement therapy with psychotherapy (Bogenschutz et al., 2015), mindfulness-based relapse prevention and alcohol education (Grabski et al., 2022), and psychotherapy with aversion therapy (Krupitsky & Grinenko, 1997).

Follow-up length varied greatly among the included studies, and the Azhari et al. (2021), Pradhan and Rossi (2020), and Lalanne et al. (2016) studies did not include a period for follow-up after the treatments. The Dakwar et al. (2017) had a noticeable short follow-up length of only 2 weeks. The other ranged from one month to three years.

Table 5: Main purpose and treatment context for the included studies. Psychedelic substance and placebo substance/intervention with dose, administration and number of times administered, as well as follow-up length.

#	Group	Main purpose	Psychedelic substance	Placebo substance/ intervention	Treatment context	Follow-up length (months)
1	Bogenschutz et al. 2015	Assessment of the safety and efficacy of psilocybin in combination with MET for AUD, and improvement on study outcomes	**Psilocybin** Dose: **0.3-0.4 mg/kg** Administration: Oral Times administered: 2	No control	12-week treatment with **MET** and **PT**	9
2	Dakwar et al. 2020	Test whether a single ketamine infusion improves abstinence and time to relapse in patients with SUD engaging in MET-treatment	**Ketamine** Dose: **0.71 mg/kg** Administration: IV Infusion length: 50 min Bolus: Ketamine/saline, 2 min Times administered: 1	**Midazolam** Dose: **0.025 mg/kg** Administration: IV Infusion length: 50 min Bolus: Saline, 2 min Times administered: 1	5-week outpatient treatment with **MET**	6
3	Das et al. 2019	Assessment of ketamine for MRM RET in harmful drinkers, reducing the reinforcing effects of alcohol and long-term drinking levels	**Ketamine** (RET+KET) Dose: **350 ng/dl** Administration: IV Infusion length: 30 min Times administered: 1 **Ketamine** (NO RET+KET) Dose: **350 ng/dl** Administration: IV Infusion length: 30 min Times administered: 1	**Saline** (RET+PBO) Administration: Intravenous Infusion length: 30 min Times administered: 1	9-month treatment with **PT** and **MRM retrieval**	9
4	Grabski et al. 2022	Investigate the safety and efficacy of ketamine compared to placebo in increasing abstinence in patients with AUD, and pilot ketamine in combination with either MBRP or AE	**Ketamine** with therapy Dose: **0.8 mg/kg** Administration: IV Infusion length: 40 min Times administered: 3 **Ketamine** with AE Dose: **0.8 mg/kg** Administration: IV Infusion length: 40 min Times administered: 3	**Saline** with therapy Dose**: 0.9 %** Administration: IV Infusion length: 40 min Times administered: 3 **Saline** with AE Dose: **0.9 %** Administration: IV Infusion length: 40 min Times administered: 3	10-visit treatment with **MBRP** and **AE**	6
5	Kolp et al. 2006	Assess whether ketamine-enhanced psychotherapy can increase abstinence rates among patients with AUD	Dose is not reported, but "the Krupitsky et al. (1992) study was used as a benchmark to guide Kolp`s work". **Ketamine** in 5 different treatment methods (double session for method 5/5) Dose: **3.0 mg/kg** Administration: IM Times administered: 1-2	No control	Five different treatment models with daily or weekly **PT**	12
6	Krupitsky and Grinenko 1997	*To assess the efficacy of Ketamine-psychotherapy in abstinence,*	**Ketamine** Dose: **2.5 mg/kg** Administration: IM Treatment length: 45-60 min	Conventional pharmacological and therapeutic treatment of AUD	3-month treatment comprising of 3 phases with **PT** and **AT**	12, 24, and 36

		compared to traditional treatment of AUD	Times administered: 1			
7	Krupitsky et al. 1992	To assess the efficacy of the Affective Contra-Attribution (ACA) method in degree of abstinence, compared to traditional treatment of AUD	**Ketamine** Dose: **3.0 mg/kg** Administration: IM Times administered: 1	Conventional pharmacological and therapeutic treatment of AUD; aversive emetic therapy, pharmacological treatment of craving, and individual and group therapy	Treatment comprising of 3 phases with **PT** and **AT**	12
8	Sessa et al. 2021	Assess if MDMA-assisted psychotherapy can be delivered safely and be tolerated by patients with AUD, as well as improve study outcomes related to abstinence and quality of life	**MDMA** Dose: **25 mg + 62.5 mg** Administration: Oral Times administered: 2	No control	10-week treatment with **PT**	9
9	Dakwar et al. 2014	Assess the effects of ketamine on SUD[2], the tolerability of two doses and how they affect cue-induced craving and motivation to quit	**Ketamine (K1)** Dose: **0.41 mg/kg** Administration: IV Infusion length: 52 min Times administered: 1 **Ketamine (K2)** Dose: **0.71 mg/kg** Administration: IV Infusion length: 52 min Times administered: 1	**Lorazepam (LZD)** Dose: **2.0 mg** Administration: IV Infusion length: 52 min Times administered: 1	9-day treatment with **relaxation** and **mindfulness-based exercises**	1
10	Dakwar et al. 2017	To detect behavioral shifts in the relative salience of cocaine now vs. money later, longer than 24 hours post-infusion	**Saline** Administration: IV Infusion length: 50 min Bolus: Saline, 2 min Times administered: 1 **Ketamine** Dose: **0.60 mg/kg** Administration: IV Infusion length: 50 min Bolus: 0.11 mg/kg ketamine/saline, 2 min Times administered: 2	**Saline** Administration: IV Infusion length: 50 min Bolus: Saline, 2 min Times administered: 1 **Midazolam** Dose: **0.025 mg/kg** Administration: IV Infusion length: 50 min Bolus: Saline, 2 min Times administered: 2	Three 6-day treatments with **verbal choice procedures** for self-administration of cocaine.	2 weeks
11	Dakwar et al. 2019	Test whether a single ketamine infusion improves abstinence and time to relapse in patients with SUD[2] engaging in MBRP-treatment	**Ketamine** (n=27) Dose: **0.5 mg/kg** Administration: IV Times administered: 1	**Midazolam** (n=28) Dose: **0.025 mg/kg** Administration: IV Times administered: 1	5-day treatment with **MBRP** and **behavioral treatment**, with additional outpatient **MBRP** during follow-up	6
12	Jovaisa et al. 2006	Evaluate the effect of subanesthetic ketamine infusion for suppressing opiate withdrawal symptoms; the long-term effects; subsequently, abstinence and post-	**Ketamine** Dose: **0.5 mg/kg/h** Administration: IV Times administered: 1	**Saline** Administration: IV Times administered: 1	5-day inpatient **OT** under **GA** with mandatory aftercare plan (**abstinence-based**, **counseling** or **rehabilitation**)	4

		infusion treatment retention				
13	Krupitsky et al. 2002	To assess the safety and efficacy of KPT for patients with OUD, using one high-dose and one low-dose group to compare psychedelic experience, abstinence, craving, and positive change in nonverbal unconscious emotional attitudes	**Ketamine** Dose: **2.0 mg/kg** Administration: IM Treatment length: 1.5-2 hrs Times administered: 1	**Ketamine** Dose: **0.2 mg/kg** Administration: IM Treatment length: 1.5-2 hrs Times administered: 1	5-day treatment with **PT**	24
14	Krupitsky et al. 2007	Assessing the efficacy of single vs. repeated session ketamine-assisted PT for abstinence, reduction in craving and positive change in nonverbal unconscious emotional attitudes	**Ketamine** Dose: **2.0 mg/kg** Administration: IM Treatment length: 1.5-2 hrs Times administered: 3	**Ketamine** Dose: **2.0 mg/kg** Administration: IM Treatment length: 1.5-2 hrs Times administered: 1	3-month treatment with **PT** and **AC**	12
15	Lalanne et al. 2016	To test opioid tapering using oral ketamine to reduce withdrawal symptoms and successfully reduce the need for opioids	**Ketamine** Dose: **1.0 mg/kg** (5.0 mg/ml) Administration: Oral Times administered: 1	No control	Gradual, monitored **OT**	No follow-up
16	Ocker et al. 2020	Test whether a multimodal, integrated ketamine-approach can promote successful opioid tapering, reduce pain, withdrawal symptoms and promote long-term abstinence	**Ketamine** Dose: **0.09-0.6 mg/kg** Administration: IV Times administered: 5-day continuous infusions **Ketamine** Dose: Up to **0.77 mg/kg** Administration: IV Times administered: 5-days continuous infusions	No control	Two 5-day continuous treatments with **OT** and **CBT**, with additional **CBT** during follow-up	12
17	Pradhan and Rossi 2020	To test the feasibility and efficacy of ketamine, rTMS, and TIMBER in patients with OUD	**Ketamine** Dose: **0.75 mg/kg** Administration: IV Infusion length: 45 min (stopped at 745 mg total) Times administered: 1	No control	**rTMS** and **TIMBER**	No follow-up
18	Azhari et al. 2021	Assess the impact of ketamine in combination with MET and MBRP on motivation to quit, reduce cravings and promote abstinence	**Ketamine** (ADM1) Dose: **0.6 mg/kg** Administration: IV Infusion length: 50 min Bolus: 0.11 mg/kg ketamine/saline, 2 min Times administered: 1 **Ketamine** (ADM2) Dose: **0.6 mg/kg** Administration: IV Infusion length: 90 min Bolus: 0.11 mg/kg ketamine/saline, 2 min Times administered: 1	No control	6-week outpatient treatment with **MET** and **MBRP**	No follow-up

19	Johnson and Black 2020	Explore the therapeutic potential of classic psychedelics in assisting with treatment of SUD (with co-occurring depression)	**LSD** Dose: **200-500 mcg** Administration: Oral Times administered: 5 ***DMT*** *Dose: **50-100 mg*** *Administration: Inhalation* *Times administered: 4*	No control	Continuous **PT** over several years, with participation in relapse-prevention program	8

Note. AC: Addiction counseling; AE: Alcohol education; AT: Aversion therapy; AUD: Alcohol use disorder; AWS: Alcohol withdrawal symptoms; CBT: Cognitive behavioral therapy; GA: General anesthesia; IM: Intramuscular; IV: Intravenous; KPT: Ketamine psychotherapy; MBRP: Mindfulness-based relapse prevention; MET: Motivational enhancement therapy; MRM: Maladaptive reward memories; OT: Opioid tapering; OUD: Opioid use disorder; PT: Psychotherapy; RET: MRM retrieval during "reconsolidation window"; SUD: Stimulant use disorder.

4.4 Study outcomes

The study outcomes for the measurements abstinence and changes in craving are summarized in Table 6, as well as report of any adverse event during the treatments. Adverse events were not reported in the Krupitsky and Grinenko (1997) and Johnson and Black (2020), while the other studies provided a short summary of the events and most did not publish complete data of any such events.

Table 6: Study outcomes for the included studies; abstinence and craving. Report of any adverse events during treatments.

#	Group	Abstinence	Craving	Adverse events (yes/no)
1	Bogenschutz et al. 2015	Significant decrease in use up to 36 weeks post treatment	From baseline mean 16.0 vs. 9-month mean 8.11 (using PACS)	Yes
2	Dakwar et al. 2020	52.9% abstinence across the 21 days post-infusion, compared to 40.9% in control	*Not reported*	Yes
3	Das et al. 2019	Significant reduction in total alcohol consumption (from baseline to 9-month follow-up) for RET+KET (23.5 UK units), some for NO RET+KET (13.6 UK units), and no for RET+PBO (4.9 UK units). Long-term reduction with no evidence of rebound. RET+KET halved their weekly consumption (84-41 UK units)	Significant reduction in reactivity (day 1 vs. day 10) in RET+KET, not in control groups	Yes
4	Grabski et al. 2022	86.5% abstinence at 6 months in ketamine-therapy group, 82.5% in ketamine-AE, 78.3% in placebo-therapy, and 70.7% in the placebo-AE group (mean difference 10.1)	No significant reduction in alcohol craving (using ACQ-NOW)	Yes
5	Kolp et al. 2006	Approximate 1-year abstinence for group 1-5: 25% vs. 35% vs. 50% vs. 60% vs. 70%	*Not reported*	No
6	Krupitsky and Grinenko 1997	65.8% abstinence at 12 months compared to 24% in control	*Not reported*	Not reported
7	Krupitsky et al. 1992	69.8% abstinence at study end (1 year) compared to 24% in control	*Not reported*	No
8	Sessa et al. 2021	Complete abstinence in 64% at 9-months. From 130.6 units/week to 0.0 at baseline and during treatment. Steady increase in	*Not reported*	No

		consumption to 6-month follow-up, and a reduction to 18.7 units/week at 9-months		
9	Dakwar et al. 2014	50% 2-week abstinence. Significant reduction in cocaine use (baseline: 22/28 days/use vs. follow-up: 5/28 days/use)	Significant decreased craving scores in K1 relative to LZP (median 65 vs. -126) and K1 relative to LZP (median 53 vs. -18) (using VAS-C)	Yes
10	Dakwar et al. 2017	67% reduction in self-administration of cocaine from baseline to 28-hours post-infusion, compared to 10% in control	Significant reduction (ca. 60%) compared to (ca. 15%) control. This was not sustained throughout the monitoring period (VAS-C)	Yes
11	Dakwar et al. 2019	48.2% abstinence at 5 weeks compared to 10.7% in control	Craving rated 58.1% lower in ketamine-group than in control group. No evidence of change over time in both groups) (VAS-C)	Yes
12	Jovaisa et al. 2006	18% abstinence at 4-month follow-up compared to 15% in control	*Not reported*	No
13	Krupitsky et al. 2002	Significant difference in abstinence between groups at 14/16 time points over 24 months, with much greater abstinence in high-dose group. 50% went back to using within the 3 first months, compared to 60% in control	Significant reduction from pre-treatment to post-treatment in both groups. 29.24 to 1.71 in high-dose group vs. 36.34 to 0.00 (n=1) in low-dose group (using VAS-C)	Yes
14	Krupitsky et al. 2007	50% 1-year abstinence compared to 22.2% in control	Significant reduction from baseline to 12 months, 20.1±4.7 to 0.3±0.2 in multiple session group vs. 22.8±5.4 to 0.0±0.0 in control (using VAS-C)	Yes
15	Lalanne et al. 2016	Dramatically reduced doses of opioid painkillers. Ketamine withdrawn without any withdrawal symptoms	No measurement for comparison were reported, other than significant craving before treatment vs. no cravings to report after treatment	Yes
16	Ocker et al. 2020	Complete abstinence throughout treatment period and 1-year follow-up	*Not reported*	Yes
17	Pradhan and Rossi 2020	*Not reported*	Baseline 23.66 reduced to 8.33 post-treatment. 65.7% decrease in craving (using OCS)	No
18	Azhari et al. 2021	75% abstinence for at least 3 weeks. Significant reduction in using days/week (baseline: 5.1 vs. post-infusion: 0.8 vs. study end: 0.5)	Significant difference in craving between baseline and study end (using VAS-C)	No
19	Johnson and Black 2020	3-year abstinence from stimulants. Reduction in cannabis consumption from daily to weekly use. Clear reduction in times used and more than 50% reduced dose of recreational psychedelics	*Not reported*	Not reported

Note. ACQ-NOW: Alcohol Craving Questionnaire; OCS: Opiate Craving Scale; PACS: Penn Alcohol Craving Scale; VAS-C: Visual Analog Scale – Craving

4.4.1 Abstinence and craving

As presented in table 6, the majority of studies have reported measures of abstinence or reduced alcohol or drug use. There is no apparent difference in abstinence based on addiction type or psychedelic substance, nor between low abstinence rates and lack of therapy or

behavioral intervention. There is, however, notably limited data on LSD, MDMA, and psilocybin compared to ketamine. The amount of data on ketamine shows a notable large difference in abstinence, reported as low as 18% in the Jovaisa et al. (2006) study, but also as high as 86.5% in the Grabski et al. (2022) study and even complete abstinence throughout the follow-up period as reported in the case report by Ocker et al. (2020). All controlled studies showed distinction between active group and control group to some extent, even as big a difference as reported in the Dakwar et al. (2017) study, with 67% vs. 10% reduction in self-administration. Kolp et al. (2006) reported abstinence from 25% to 70%, by using the results from the first studies to improve and compile a treatment model which maximizes the effects from ketamine and psychotherapy.

All studies that measured craving reported significant reduction, except for the Grabski et al. (2022) study with no significant reduction reported. In the controlled studies, we see a noticeable smaller reduction in craving between active and control in those using low-dose versus high-dose psychedelic substances (Krupitsky et al., 2002), and multiple sessions versus single session with psychedelic substances (Krupitsky et al., 2007), compared to those using comparably more different control substances or interventions (Dakwar et al., 2017; Dakwar et al., 2019).

4.4.2 Mindfulness and self-efficacy through spiritual and mystical experiences

Several authors have contributed much of the research's success in promoting and maintaining abstinence to hallucinogens unique ability to increase mindfulness, spirituality, feeling of unity, and self-reflection through spiritual and mystical experiences (Krupitsky et al., 2002; Krupitsky et al., 1992; Pradhan & Rossi, 2020; Sessa et al., 2021). Bogenschutz et al. (2015) identified a strong correlation between the measured effect of the psilocybin induced psychedelic experience, and clinical outcomes (e.g., reduced alcohol consumption), indicating that a greater psychedelic experience promotes greater rates of abstinence. This was also confirmed in the Krupitsky et al. (2002) study, that found greater abstinence in the high-dose group who reported a complete psychedelic experience, than the low-dose group who only reported sub-psychedelic experiences. Krupitsky et al. (2002) also reported increased spirituality and understanding of one self's meaning and purpose of life, self-efficacy became more "internal", and so-called non-verbal unconscious emotional attitudes significantly improved in both high-dose and low-dose groups. Full psychedelic experiences were also reported in the Johnson and Black (2020) study, where the case reports single participant

claimed that his use of classic psychedelics had given him insight and awareness enough to face the problematic behavior, as well as his personal discovery of spirituality.
MDMA also elicits psychedelic experiences, but these experiences and drug effects are normally better tolerated than classic psychedelics, as reported by (Sessa et al., 2021) in their study with MDMA for alcoholics. At the same time, the mystical or spiritual aspects of the experience were reported to increase mindfulness so that, coupled with increased feelings of empathy and compassion for others and oneself, could improve self-awareness and as a result reduce or remove the denial of the harmful behavior (alcohol abuse) (Sessa et al., 2021).

4.4.3 Depression and anxiety

As mentioned, the participant in the Johnson and Black (2020) reported increased insight and awareness following psychedelic experiences, which in turn gave improved cognitive flexibility for more sustainable problem-solving attitudes and removal of the "victim-mentality" that previously fueled his addiction. More importantly, he stated that psychedelics gave him the insight needed to manage his symptoms of depression, which was all but removed during the follow-up period (Johnson & Black, 2020). Several other studies have also reported decreased depression and anxiety (Azhari et al., 2021; Bogenschutz et al., 2015; Dakwar et al., 2014; Grabski et al., 2022; Krupitsky et al., 2002; Sessa et al., 2021).
Reduced anxiety, depression, and symptoms of anhedonia was reported by Krupitsky et al. (2002) – with no significant difference between high-dose and low-dose group. They also measured improvements in several categories of nonverbal unconscious emotional attitudes related to self-image, motivation, hopes, and connection to others – which in turn are reported to be important tools in managing depression and anxiety (Krupitsky et al., 2002). It`s worth mentioning that this decrease in depression was not sustained over time as reported in some studies with substantial follow-up (Bogenschutz et al., 2015; Sessa et al., 2021).

5.0 Discussion

The purpose of this review was to identify and map published studies treating addiction with pre-selected psychedelic substances, in a therapeutic or clinical context with a behavioral outcome or therapeutic gain. Subsequently, identify limitations and knowledge gaps with the conducted research and then introduce possible strategies to inform future research in Norway and elsewhere.

Surprisingly, only 13 studies were first identified within the limitation of being performed in a therapeutic context exclusively. Six additional studies were included during the last comprehensive search where studies performed in a clinical context with a behavioral outcome or therapeutic gain were included. Regardless, this resulted in a sample containing fewer studies than first anticipated, especially studies researching the classic psychedelic substances (LSD and Psilocybin) and MDMA. In hindsight, this seems logical considering the restrictions the substances are under and how much funding is needed to plan and perform clinical research like this. Still, the current research with LSD, psilocybin, and MDMA serves as a great foundation for future addiction research. To our surprise, there is substantially more research done on ketamine, both as an active substance in combination with therapy or behavioral interventions, as well as a general anesthesia used during detoxification to reduce withdrawal symptoms. As this is not categorized as a classic psychedelic compound, and was not publicly advertised as a commonly used recreational drug prior to the psychedelic shut-down, research restrictions have not been as strict as with the other substances included for this review. Ketamine is classified as a schedule III substance and available through prescription, which makes it easier to obtain and utilize. As 16 of the 19 included studies utilized ketamine, this provides a substantial amount of data to evaluate the substance`s potential in treating addiction, and could perhaps be the substance of biggest interest to implement in future addiction-research. Noteworthy, there are significant methodological differences between the included ketamine-studies, which could limit systematic comparison.

5.1 Abstinence and consistency in outcomes

The outcomes for abstinence and changes in craving are important when evaluating whether the treatments are effective long-term. Moreover, reduced craving can increase motivation and ultimately increase treatment outcomes in the long run. However, these outcomes have been inconsistently reported in the included studies, and limit systematic evaluation and comparison. An example can be seen in the Pradhan and Rossie (2020) study, where the

researchers aimed at evaluating the efficacy and feasibility of their treatment combination of ketamine, rTMS, and TIMBER, through measuring reduced craving and increased mindfulness. This is interesting, but it does not report the participants' reduced intake of opioids, obtained abstinence, or maintenance of abstinence

As already emphasized, this review provided little data on LSD, psilocybin, and MDMA. However, the impressive abstinence outcomes serve as excellent proof for continued research. Abstinence outcomes differ significantly more for the ketamine studies, ranging from 18% to 86.5%, or even complete abstinence. There does not seem to be any difference in abstinence based on addiction type or psychedelic substance, but this is difficult to decide with the methodological differences. Whereas eleven of the ketamine studies were controlled and used some form of control substance or intervention, neither of the studies using the other substances used controls. It is difficult to say how much this affects the results, especially since the controls used are significantly different, ranging from single control groups with saline infusions, to multiple control groups to evaluate both the intervention and the psychedelic substance alone and in combination with each other. This is also affected by how abstinence is measured, as the method and context it is measured in, differ greatly from study to study. Abstinence rates might also change over time or use some time to stabilize, as seen in some of the included studies (Das et al., 2019; Sessa et al., 2021), which means that a substantial follow-up period is necessary to evaluate treatment efficacy. Consistently reporting of abstinence outcomes and a substantial follow-up period should lead to better comparison between interventions. Therefore, this review strongly recommends the inclusion of abstinence as a study outcome. This will build the evidence base, resulting in more meaningful research and recommendations.

5.2 Methodological limitations and the synergy aspect

There are methodological differences and inconsistencies in applied treatments among participants that might contribute to the differences seen in treatment outcomes, as well as limit any comparison between the studies. With the current presented research, it is difficult to understand which treatments lead to what effect. More specifically, how much the administration of psychedelics versus the application of behavioral interventions contribute to the study outcomes, and if there is a possible synergy between the intervention and psychedelic substance. The synergy aspect is discussed by many, concluding that more research is needed to establish evidence (Das et al. 2019; Bogenschutz et al. 2015; Sessa et al. 2021; Dakwar et al. 2019). The figurative psychological landscape created by the

psychedelic substance indicates the need for the right tools to navigate said landscape correctly, and to achieve behavioral change. The patient is more susceptible to change while under the influence of psychedelic substances, but it is impossible to say how easy or challenging it is to achieve positive change without guidance.

This review presents evidence in favor of, as well as against, this synergy aspect. Two studies that did not use any form of therapy or behavioral interventions in their treatments presented impressive study outcomes (Jovaisa et al., 2006; Lalanne et al., 2016). This might indicate that implementing the substances is effective on its own. However, the short follow-up in these two studies makes it difficult to evaluate any long-term effects from the treatments. In addition, the study with the lowest abstinence rates for both active and control (18% versus 15%) provided behavioral treatment through a mandatory outpatient aftercare program: abstinence based, counseling or rehabilitation (Jovaisa et al., 2006). In other words, the behavioral treatments were administered after the treatments, limiting the possibility of synergy. This synergy aspect was investigated further by researcher Ravi Das and colleagues (Das et al. 2019), by dividing their participants into three groups, they evaluated whether ketamine during retrieval of maladaptive reward memories can successfully interfere with these memories and promote behavioral change. The group receiving ketamine with retrieval had significantly greater reduction in alcohol consumption than both the group receiving ketamine without retrieval, and the group receiving placebo with retrieval. This is also seen in the other controlled studies, but not all provided the same kind of behavioral treatment for both psychedelic-active and placebo-control groups, so there is limited comparable data to evaluate how significant this difference might be.

To summarize, a more suitable study design should allow for measurement between the psychedelic treatment and the behavioral intervention, and subsequently, evaluate the possibility of synergy. It is recommended to include more than one control group for future research, for instance by including one active control group receiving only the behavioral intervention, and one control group receiving only the psychedelic intervention.

5.3 Checklists, strategies and guidelines for psychedelic research

As the research conducted prior to the psychedelic shut-down have been heavily critiqued, several researchers have addressed these flaws and presented checklists (Petranker et al., 2020), strategies (Rucker et al., 2018), and guidelines (Johnson et al., 2008) for conducting psychedelic research.

Petranker et al. (2020) proposed a checklist to ensure transparent research conducted with clear and concise standards, as well as to highlight limitations and ensure that funding, time, and effort is well spent. The level of details provided for the publicly available material for all the included studies varies greatly, which in turn makes it difficult to replicate the studies and build on their progress. Petranker et al. (2020) highlighted pre-registration of the trials prior to its execution, with analysis plan and treatment protocol, as well as making all data and material available and published. Extensive research could only find that three of the included studies have provided this (Azhari et al., 2021; Dakwar et al., 2020; Grabski et al., 2022), but it does not, however, mean that other researchers cannot contact the head researcher of each individual trial and receive this extra information. An example of limited available information is the lack of reported dose of administered ketamine during the treatments in the Kolp et al. (2006) study, which makes it difficult to evaluate optimal dose for future research. When analyzing the included studies, seemingly only five have published additional documents with supplementary data from the trial (study # 2-4 and 18-19), publicly available without the need to contact the researchers. Many studies did, however, provide a detailed method section with much information needed to provide a mental picture of the treatments, but there is no doubt that the information provided is too lacking to replicate the studies and extend on the research, as is necessary according to Petranker et al. (2020) to ensure transparency.

The research strategy proposed by Rucker et al. (2018) for conducting psychedelic research also addresses the lack of transparency, specifically the lack of comprehensive data of outcomes and adverse events, in the research conducted prior to the psychedelic prohibition. Six studies did not provide systematic information of any adverse event or effects that might have occurred during the treatments, which have been previously documented to be liable risks associated with these substances (Rucker et al. 2018). It seems highly crucial to make any possible adverse events publicly available, to better predict and prepare for anything that could happen during the treatments, and to some extent even prevent them from happening. The inconsistent reporting of adverse events is therefore questionable, especially since the importance of this is something that has also been emphasized in older publications, such as the research guidelines for psychedelic research published by Johnson and affiliates in 2008 (Johnson et al. 2008). These guidelines are of course of no means obligatory guidelines for those conducting psychedelic research, but limitations with previously conducted research (pre-prohibition) have been mentioned in several of the included studies, so it is questionable why this has not been addressed further in the post-prohibition research. This will perhaps be

less evident in some of the ongoing psychedelic research funded by MAPS, who have several multi-site trials in different countries and in that way connects researchers and provides a platform for transparency, communication, and cooperation (MAPS, 2022).

The safety-guidelines proposed by Johnson and affiliates emphasizes the importance of safety-related selection criteria, especially contraindicated psychosocial function and concomitant drug use. Some mental disorders such as schizophrenia, psychotic disorders, and bipolar disorder are contraindicated in psychedelic studies, as their reaction to the experience can be volatile and unpredictable (Johnson et al. 2008). This will mainly ensure the participants safety, but by including a more homogenous group without individual psychiatric diagnosis`, it will also be easier to eliminate counter-interactions and predict study outcomes for the general population. Such contraindicated psychosocial function can be identified through psychological screening prior to study start, but this should be defined by the nature of the study according to Johnson et al. (2008). Psychiatric comorbidities were inconsistently applied in the included studies, and were not reported in three. Any additional medication could potentially alter the effects from the psychedelic substances by both increasing or decreasing their effects, or by creating new and unpredictable reactions. We do not know if the study outcomes can be contributed by the additional medication, or if perhaps the presence of certain mental health disorders in combination with addiction decreases the effect from the treatments. It is therefore beneficial to mainly include otherwise healthy participants without any additional psychiatric comorbidities or medication, as too little is known about what impact they might have on the compounds and the treatment outcomes.

Several of the included studies also have reports of patients with additional depression and/or anxiety that have benefited profoundly from the psychedelic treatments. The characteristics and functionality of the substances` antidepressant effects are still not completely understood, as is their role in treating addiction. It is not uncommon for addicts to also struggle with depression and anxiety, or other more severe mental disorders. But then it is also important to clearly define and report these participant characteristics and qualities, as we do not know what kind of impact the absence or presence of these additional diagnoses might have on the treatment outcomes, or whether any findings can be extended to the general population (Petranker et al. 2020). Variations within the same treatment groups could perhaps to some extent be contributed by dissimilarities in participant characteristics, seen in groups where some have additional psychiatric comorbidities, and some do not. Heterogeneous groups where, for instance, some of the participants have psychiatric comorbidities while the rest do

not, is something to avoid (if possible) when implementing psychedelic-assisted addiction research.

Inconsistencies when defining the treatment groups have also been accentuated by Rucker et al. (2018), and how it can even result in selection bias. It's important to remember that participants might present with different levels of motivation and adherence to the treatments based on mental, physical, and social factors, for instance, additional psychological disorders. This can be seen in the Krupitsky and Grinenko (1997) study, where the participants could volunteer for the psychedelic treatments. The lack of randomization between active and control groups could potentially introduce some selection bias, as the group receiving the psychedelic treatments might have more motivation to obtain and maintain sobriety than the control group. For the Krupitsky and Grinenko (1997) study, this is a limitation that might have given lower abstinence rates for the control group than it potentially could have with proper randomization. Whether the patients are treatment-seeking and have a diagnosis or not can also impact their motivation to maintain abstinence. Those who have acknowledged their disorder and are actively trying to change have perhaps come a long way and are more motivated than those who have not progressed so far as to see the need or want to change. Such bias can also be present when there are great differences in participant characteristics within the same group, for instance, groups containing participants who use different medications or have different mental states. It is therefore recommended to put extra effort into making homogenous groups without additional characteristics that can affect the treatment outcomes, ensure randomization, and control groups to limit any bias, and include participants with similar characteristics in both the active and control groups.

5.4 Public health relevance

We see more evidence of increased alcohol consumption among men and the younger part of the Norwegian population. Those with dependencies and addiction diagnoses are regularly those with low socioeconomic status and limited means and money to not only seek out and complete treatment, but also maintain their sobriety after. More recently, we also see an increase in alcohol consumption among those with higher income and higher education, perhaps indicating that the disorder is proliferating to a larger part of the population. Even though alcohol and drug related deaths fluctuate, both decreases and increases from time to time, it is apparent that over-consumption of alcohol and drugs are a lasting public health problem that need to be addressed.

It will be important to conduct research with interventions contextualized to the public health field to help address this issue, and evidently there is much to be learned from research conducted abroad. The hope is that psychedelic-assisted addiction treatments can address this issue and contribute with new insight, strategies, and protocols for treating addiction disorders, that can be used to inform the policy makers within the public health field. These interventions could potentially be paralleled to the treatment of other mental health disorders, such as MDD or PTSD. A scope of the field would therefore highlight any limitations with previously conducted research that can be addressed and avoided, as well as provide recommendations for implementation of psychedelic-assisted addiction treatments in Norway. For future research, this review strongly recommends including relevant outcome measurements, more specifically abstinence rates, that should be measured continuously throughout a substantial follow-up period. This allows for documentation of long-term effect after treatment and provide evidence of treatment efficacy. The use of more than one randomized control group is recommended to investigate possible synergies between substances and interventions, as well as limit any bias or difference in motivation to complete the treatments. It would be beneficial to include homogenous treatment groups without additional characteristics that potentially could affect the treatment outcomes or cause unpredictable adverse events, such as psychiatric comorbidities or concomitant drug use. Ultimately, all data and materials from the trials should be made available to ensure transparency and progress in the field. This will build a strong evidence base, resulting in more meaningful research and recommendations.

5.5 Limitations

There are several limitations with this review. Much time and effort were invested in the development of the search strategy and inclusion criteria, to identify as many relevant keywords as possible, and use different combinations of keywords and concepts to build the query for the search strategy. The treatment contexts included for this review was edited during the search process to include studies performed in a clinical context, predominantly to attain a larger data collection, and subsequently widened the scope for this review. This resulted in a data collection with noticeable methodological differences and deviating aims, which could not have been possible with the use of a stricter evidence synthesis approach.

The development of the search strategy and inclusion criteria was iterative in comparison with what is recommended by the JBI guidelines (Aromataris & Munn, 2020), thus less systematic.

But as this is a scoping review, and that the field is relatively new and unexplored, it is more acceptable that the development of a search strategy and inclusion criteria can be iterative.

As this is a master thesis, there was only one reviewer, but everything was closely discussed with the supervisor. Nevertheless, having only one reviewer makes the research more prone to subjectiveness and human error. When screening the results uploaded to EndNote after the database searches, there is also the possibility of error. Important information and interesting studies or articles could have been excluded prematurely during the screening of titles, if they seemingly lacked relevance to this review's concepts. The included studies are also limited to those with publications in English, Norwegian, Swedish, and Danish. This means that some possibly relevant articles/studies were excluded for missing eligible translation.

The field is relatively new and unexplored, making it difficult to find general definitions or concepts. Interpretation of broad concepts, such as context, is affected by subjective definitions or understanding. It is therefore possible that relevant studies could have been excluded based on inconsistently defined terms and descriptions.

5.6 Ethical considerations

This scoping review retrieved and analyzed data from previously published studies, where the primary researchers have obtained informed consent by the participants. As no primary data has been collected for this review, there has been no need to report the project to Norsk Senter for Forskningsdata (NSD) to evaluate whether any personal information can identify either of the participants (NSD, n.d.), or apply any plans for primary research to Regionale komiteer for medisinsk og helsefaglig forskning (REK) (REK, n.d.). However, if I found that a literature search did not give enough information to perform the scoping review, the plan was to perform expert interviews. This implies gathering sensitive information that in some cases can identify the participants, resulting in concerns regarding informed consent, anonymity, and confidentiality (Fossheim, 2015).

Conducting expert interviews emphasizes the research rather than the participants in the study, diverting the focus from the more sensitive personal information that could potentially raise the question regarding anonymity and confidentiality. Still, all participants in the interviews and those mentioned during the interviews, would be given fake names or numbers, as well as other measures to ensure everyone's anonymity. Since this current study is not a protocol, a treatment or a strategy, and the participants in the study would not be interviewed, there would be no need to apply to REK. The interviews would be recorded for

continued use in this study, and since these can never be fully anonymized, I would have needed to apply to NSD for consent (Fossheim, 2015).

5.7 EHS: Risk assessment

A risk assessment needs to be performed before any study can commence. This is done to map any aspects that can go wrong during the study, preventing misunderstandings, damages, sickness, or anything that can affect the environment, health, and safety (EHS) of those involved. When conducting primary research, it`s important to identify anything that can cause physical damage, such as chemicals, fire, fall accidents, or exposure to loud sounds. This also extends to any material damage, especially damage to equipment. Any potential psychological impacts also need to be assessed beforehand, which is especially important in studies researching different types of psychotherapy for mental disorders (The Claremont Colleges, 2021). As this is a scoping review where the only data collected is secondary, the need for a risk assessment did not apply.

6.0 Conclusion

This review has highlighted the current research status for psychedelic-assisted addiction treatments performed after the psychedelic prohibition. There is limited research utilizing the classic psychedelic substances (LSD and Psilocybin) and MDMA, as receiving approval for conducting trials with human participants is a lengthy process dictated by strict regulations. However, there is comprehensive research on ketamine`s potential in addiction treatments, which serves as a great foundation for future research in Norway and elsewhere.

Moving forward, in will be important to emphasize and strive for consistency in outcomes and methodological rigor, with a substantial follow-up period to identify trends and long-term treatment maintenance. The synergy aspect can be further investigated by introducing more than one control group, and should be strengthened with randomized groups and participants with homogenous characteristics. Future research should take into account the published checklist, guideline, and strategy presented in this review, which addresses limitations with the research conducted prior to the psychedelic prohibition.

Norway is participating in multisite trials investigating other mental health disorders,

As Norway is partaking in multisite trials investigating other mental health disorders, and outcomes from the included studies for this review shows promise and need for further research, there should be no contraindication for why the Norwegian research community should not take part in the psychedelic renaissance and contribute with its knowledge and resources to improve addiction treatments.

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Journal article: “Psychedelic-assisted research for the treatment of drug and alcohol addiction: a scoping review”

Introduction

Addiction is a prominent and lasting public health problem with somber statistics that are often associated with physical, mental, social, and economic problems. The World Drug Report of 2021 showed an increase in the use of alcohol, cannabis, pharmaceutical opioids, and sedatives, as reported by addiction medicine professionals from around the world (UNOCD, 2021). Treatment options are limited, especially for those who conventional pharmaceutical (e.g., methadone, buprenorphine, naltrexone, or disulfiram) and behavioral (e.g., psychotherapy, Mindfulness-based Relapse Prevention – MBRP, Cognitive Behavioral Therapy- CBT, and Motivational Enhancement Therapy - MET) interventions have little to no effect (Nigam & Pandurangi, 2021). In addition, only about half of the countries in the world have methadone available as a treatment option for those struggling with opioid dependence (WHO, n.d.). Therefore, researchers and medical practitioners have voiced a need for new and improved medical treatments for a range of mental health disorders, including addiction, that lack available medicine or treatment options for those resisting treatment (Belouin & Henningfield, 2018).

Psychedelics, also known as hallucinogens, is a group of diverse substances that show great promise in treating numerous treatment-resistant mental health disorders, among them addiction (Belouin & Henningfield, 2018). Through animal studies, lysergic acid diethylamide (LSD) and psilocybin, considered classic psychedelics, have indicated a positive effect on the ability to learn, adapt, and understand - all important aspects when seeking behavioral change towards sobriety (Rieser et al., 2021). 3,4-Methylenedioxymethamphetamine (MDMA) is not technically a classic psychedelic substance, but it is known to induce hallucinogenic effects at high doses (Sessa, 2019). MDMA is associated with decreased fear response, increased motivation, and self-awareness, which makes it the perfect drug for avoidance behaviors, as it lowers the barrier that makes confrontation of negative emotions less stressful and daunting (Sessa, 2019). The phencyclidine derivative known as ketamine is, also not technically a classic psychedelic, most known and used as an anesthesia (Kolp et al., 2014). Preliminary research has shown ketamine’s potential in reducing and terminating cue-induced craving, subsequently resulting in greater abstinence outcomes (Dakwar et al., 2014; Das et al., 2019). Even though there are some differences in pharmacological function, what they all have in common is that the substances, potentially, make the patient susceptible to behavioral change through the creation of a psychological, figurative, landscape (Nigam and Pandurangi, 2021).

As psychedelics were attracting attention due to its increasing use in clinical trials for different mental health disorders, there was also a rise in recreational use in the 1950s and 60s (Bogenschutz & Johnson, 2016). As a result of this and increasing political unrest, all clinical research on psychedelics was stopped with the enactment of the Controlled Substances Act in 1962 (Nichols & Walter, 2021), known as “the psychedelic shutdown” or “the psychedelic prohibition”. LSD, psilocybin, and MDMA were classified as Schedule I drugs, highly restricted compounds (Bogenschutz & Johnson, 2016), while ketamine were classified as a Schedule III drug, with some restrictions for clinical research (Kolp et al., 2014). In the following decades, much was achieved in animal studies utilizing psychedelics, which subsequently resulted in important findings for future research (Alper et al., 2018; Katsidoni et al., 2011; Nichols & Walter, 2021; Vaidya et al., 1997). These promising results led to reinvestigation of psychedelics' role in addiction treatment. Both MDMA and psilocybin have received “breakthrough therapy” status by the FDA and are now under investigation for a range of mental health disorders (Nigam & Pandurangi, 2021)(Nigam and Pandurangi, 2021; MAPS source). Ketamine received FDA approval for clinical research and was made available with prescription (Nigam & Pandurangi, 2021). LSD is also under investigation for treating anxiety related to life-threatening illnesses (MAPS source).

During the pre-prohibition period of psychedelic research, there were no regulations and limited access to guidelines or generalized methods. Because research with such unique substances was relatively new, it showed endless potential and opportunities for different modes of usage. This earlier research is now criticized for severe methodological flaws that makes it difficult, or even impossible, to draw conclusions from, or extend the research to larger sample sizes (Rucker et al., 2018). Rucker et al. (2018) especially highlighted inconsistently defined treatment groups, inconsistently applied treatments among groups, lack of control groups, blinding, and validation of outcome measures, as well as missing report of adverse events and outcome data, statistical analysis of the results, and power calculations to estimate sample sizes needed to detect effect. These flaws have been addressed by many post-prohibition research strategies, introducing strategies (Rucker et al., 2018), checklists (Petranker et al., 2020), and safety guidelines (Johnson et al., 2008) for conducting psychedelic research. These ensure the safety of all participants, transparency, and provide grounds for comparison and extension of the research. Hopefully, by using guidance and principles from these articles, it should provide a higher scientific standard with research that is rigorous and transparent (Petranker et al., 2020).

Research with psychedelics have flourished since the reinitiation and it was made possible to conduct clinical trials with selected psychedelic substances. We are interested in the research specifically targeting substance abuse. This is relatively new, and we will therefore scope the field to understand the type of research that uses psychedelics for treating substance abuse. In doing so, this scoping review will synthesize the available evidence on selected psychedelic substances used for treating addiction to alcohol and other illicit substances. The aim is to present an overview of relevant studies performed after the reinitiation in the 90s, which will cast a light on the current research context. The scoping review will identify and chart knowledge gaps, limitations with previously conducted research and present potential strategies to inform research of psychedelics.

Method

The JBI Manual for Evidence Synthesis for methodological guidance was utilized in this scoping review (Aromataris & Munn, 2020). The aim was to create an overview of available evidence on the pre-selected psychedelic substances used in addiction treatment for alcohol and narcotic substances, as well as identify knowledge gaps and limitations with previously conducted research.

Search strategy

The search strategy was inspired by the JBI Guidance for conduction scoping reviews (Peters et al., 2020). Initial knowledge on the subject and keywords sourced from articles identified in preliminary searches were used to build a comprehensive search that was executed in the following databases: *Ovid Medline, Embase (Ovid), APA PsycInfo, Scopus,* and *Web of Science*. The search strategy is divided into eight concepts containing keywords and synonyms for each (MDMA, LSD, psilocybin, ketamine, classification, problem, and intervention). The initial final search executed January 29th did not present the desired amount of data to conduct the scoping review, so an additional comprehensive search was executed February 11th, where a Boolean operator was changed from "AND" to "OR" between the "substance" concepts and "classification" concept. All resulting literature was uploaded to EndNote 20 (Clarivate Analytics, PA, USA) in a separate library, before it was merged with the previous library for the first comprehensive search for further screening. The titles were screened to exclude non-eligible studies before screening the abstracts. Studies that seemingly

met the inclusion criteria were read full-text and assessed in detail against the inclusion criteria before they were included for this review.
In addition to citation searching of the included studies and reviews identified in the database searches, the following registers, databases, or social networks were used to find additional studies: REK-database (REK, n.d.), MAPS-register (MAPS, n.d.), Clinicalgovtrials.gov (U.S. National Library of Medicine, n.d.), and Research Gate (ResearchGate, n.d.). The studies identified in these databases were only included if the research had been published and presented with a clear treatment plan and results, as well as within the inclusion criteria.

Study selection

Due to the interdisciplinary nature of the topic and the relatively recent emergence of psychedelics in psychotherapy, a broader approach was preferred over a systematic quality assessment. Scoping reviews are particularly useful when the aim is to map the literature, and not to evaluate the quality of included studies or to measure a specific health outcome after an intervention. A broader scope allows for inclusion of more studies, but some restrictions were put on the search to ensure the material was within the scope of the reviews purpose.

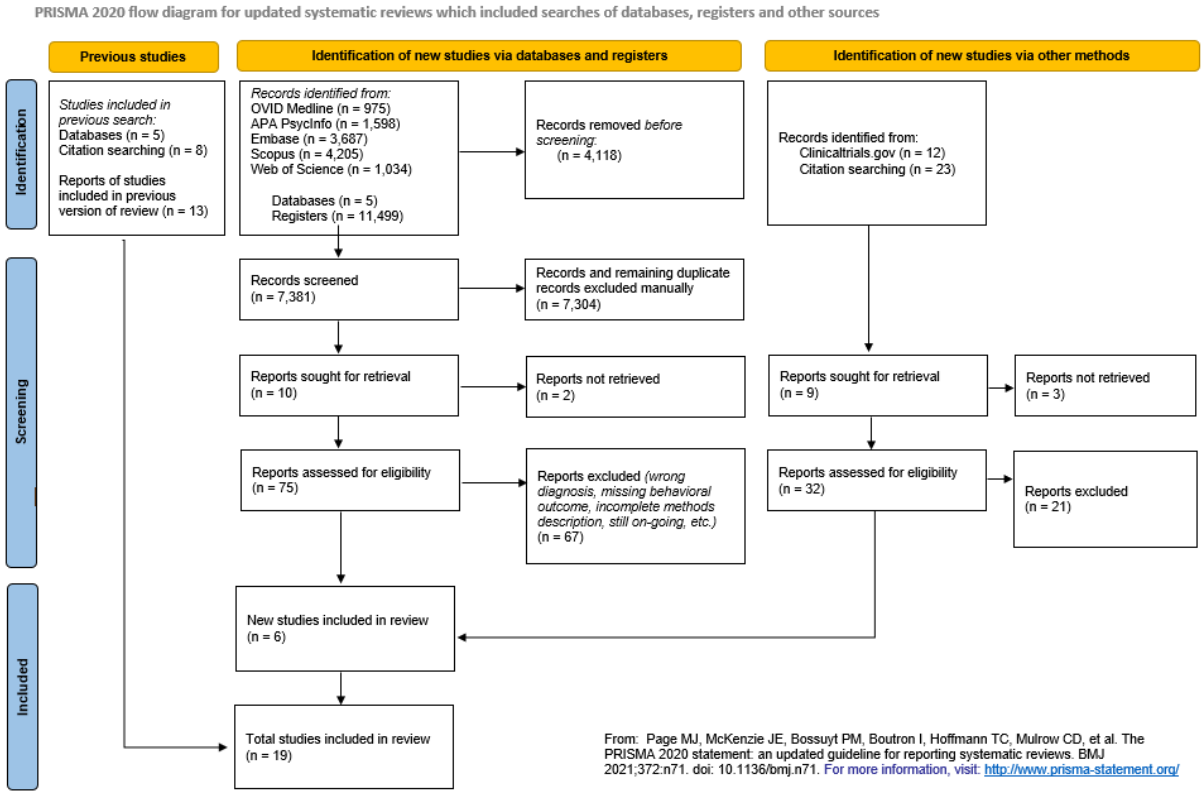
Eligibility criteria

Included studies met the following criteria: (I) published in English, Norwegian, Swedish, or Danish, (II) human participation in the trial(s), (III) participants with an addiction to alcohol or drugs, (IV) both treatment seeking participants and those not motivated for treatment, (V) utilizing LSD, psilocybin, MDMA, or ketamine in their treatment regimen, (VI) measuring outcome(s) relevant to behavior, therapy, or addiction, and (VII) studies performed and published after the psychedelic prohibition, from the 1990s.
Studies without a clear treatment plan or documentation of treatments were excluded. Reviews, summaries, meta-analysis, opinion papers, letters, and symposiums were excluded if they lacked treatment plans or documentation. Research into other mental health disorders (e.g., major depressive disorder or schizophrenia) were excluded, but studies who included participants with psychiatric comorbidities but were only targeting their addiction, were included.

Data charting and presentation

The search decision process is presented as a flowchart in Figure 1, inspired by the PRISMA 2020 flow diagram (Page et al., 2021), including search results from selected databases, removed duplicates, successful retrievals, and additional studies found through citation searching or other additional sources. It also includes the identified studies from the first comprehensive search January 29th. Information deemed relevant by the inclusion criteria was extracted from the included studies using a self-made tool for the data charting procedure. The data charting tool were comprised of elements important to establish a clear and detailed picture of the treatments, to highlight similarities and dissimilarities, and to address known limitations with the research, highlighted through evaluations of the pre-prohibition psychedelic research. This procedure and the a priori data charting tool were pilot tested to make sure all relevant data was included for the analysis and to avoid misinterpretations. The final data charting tool consisted of "group", "source", "study period", "study location", "type of addiction", "population", "study design", "psychedelic substance", "behavioral outcome", "timeline for treatment/intervention", "primary outcome", "secondary outcome", and "authors conclusions, interpretations, and recommendations" from the a priori data charting tool, supplemented with "trial identifier", "diagnosis (with diagnostic criteria)", "concomitant drug use", "psychiatric comorbidities", "purpose", "control substance", "pre-registration", "adverse events", "study measures", and "additional relevant information" for the final data charting procedure. The data gathered with the data charting tool was then synthesized and presented in relevant tables to make it possible to map and compare the included studies, and to systematically divide and visualize the data. The extracted results prepared in tables can be found under results.

Figure 1: Search decision from the final comprehensive search presented as a flowchart, inspired by the PRISMA 2020 flow diagram (Page et al., 2021). Updated version including reports from previous search (January 29th) and the last search (February 11th).



Note. From: Page M. J., McKenzie J. F., et al. (2020). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. Doi: 10.1136/bmj.n71.

Results

A first comprehensive search identified 13 studies. To achieve a broader scope of the field, the search strategy was revised and adapted to include studies in a clinical setting, investigating a therapeutic treatment of addiction and presenting behavioral or psychological outcomes. Through this additional search, another six studies were identified for inclusion, completing the search process with a total of 19 included studies (Figure 1)

General study description

The study characteristics are presented in Table 1. Of the 19 included studies, eight investigated alcohol abuse (study # 1-8), three cocaine abuse (study # 9-11), six opioid abuse (including heroin and prescription opioids) (study # 12-17), one cannabis (Azhari et al.,

2021), and one polysubstance abuse (stimulants, cannabis, and classic psychedelics) (Johnson & Black, 2020).

Most studies were conducted in the US (study # 1-2, 5, 9-11, and 16-18) or Russia (study #6-7 and #13-14), the latter utilized ketamine for different addictions under the supervision of one researcher, Evgeny Krupitsky MD, PHD. Another recurring researcher is Elias Dakwar MD, who either was the lead investigator or a co-author for the majority of the trials executed in the US (study #2 and 9-11).

Study dates were not reported in six trials (study # 6-7, 13-14, and 16-17), with the remaining studies being performed between 1996 and 2020, and the majority performed after 2010 (ref. Table 1).

Study design distribution comprised of one empirical observational study (Kolp et al., 2006), three case reports(study # 15-16 and 19), four proof of concept studies (study # 1, 8, and 17-18), and 11 clinical trials at different stages (study # 2-4, 6-7, and 9-14), all with some form of control substance and/or intervention.

Table 1: General study description including addiction-type, study design, location, study period, transparency, and number of participants.

#	Group	Addiction	Study design	Study location	Study period	Pre-registration, open data and open materials	Participants, n
1	Bogenschutz et al. 2015	**Alcohol**	Open label, proof of concept study	Albuquerque, USA	2012 – 2014	No	10
2	Dakwar et al. 2020	**Alcohol**	Triple-blind, randomized controlled pilot trial	New York, USA	2014 – 2017	Yes	40
3	Das et al. 2019	**Alcohol**	Single-blind, randomized controlled trial	London, UK	2015 – 2018	No	90
4	Grabski et al. 2022	**Alcohol**	Double-blind, randomized controlled phase II trial	London, UK	2016 – 2020	Yes	96
5	Kolp et al. 2006	**Alcohol**	Empirical clinical observations	USA	1996 – 1999	No	70
6	Krupitsky and Grinenko 1997	**Alcohol**	Non-randomized clinical trial	St. Petersburg, Russia	Not reported	No	211
7	Krupitsky et al. 1992	**Alcohol**	Randomized clinical trial	Russia	Not reported	No	186
8	Sessa et al. 2021	**Alcohol**	Open label, proof of concept feasibility study	Bristol, UK	2018 – 2020	No	14
9	Dakwar et al. 2014	**Cocaine**	Triple-blind, randomized controlled crossover trial	New York, USA	2011 – 2012	No	8
10	Dakwar et al. 2017	**Cocaine**	Double-blind, randomized	New York, USA	2013 – 2015	No	20

			controlled crossover trial				
11	Dakwar et al. 2019	**Cocaine**	Randomized controlled trial	New York, USA	2011 – 2016	No	55
12	Jovaisa et al. 2006	**Opioids**	Double-blind, randomized controlled trial	Vilnius, Lithuania	2003 – 2006	No	50
13	Krupitsky et al. 2002	**Heroin**	Double-blind, randomized controlled trial	St. Petersburg, Russia	Not reported	No	70
14	Krupitsky et al. 2007	**Heroin**	Double-blind, randomized trial	St. Petersburg, Russia	Not reported	No	59
15	Lalanne et al. 2016	**Opioids**	Case report	Strasbourg, France	2015	No	1
16	Ocker et al. 2020	**Opioids**	Case report	Philadelphia, USA	Not reported	No	1
17	Pradhan and Rossi 2020	**Opioids**	Open-label, proof of concept study	Camden, USA	Not reported	No	3
18	Azhari et al. 2021	**Cannabis**	Single-blind, uncontrolled proof of concept trial	New York, USA	2016 – 2018	Study protocol, not analysis plan	8
19	Johnson and Black 2020	**Stimulants and cannabis**	Case report	Australia	2015 – 2019	No	1

Participant characteristics

Table 2 summarizes participant characteristics to highlight psychiatric comorbidities, medication, or other characteristics that potentially could affect the treatments, or make a comparison of the outcomes difficult.

Of the included studies, four (study # 3, 6-7, and 16) did not report a formal diagnosis, and four (study # 6-7, and 16-17) did not report using a specific form of diagnostic criteria for their participants, such as the Diagnostic and Statistical Manual of Mental Disorders (DMS), International Classification of Diseases and (ICD), Alcohol Use Disorders Identification Test (AUDIT), or urine toxicology screening.

One study with 70 participants (Kolp et al., 2006) and one with three participants (Pradhan & Rossi, 2020) did not report gender distribution. Among the 920 participants in the 17 remaining studies, 758 (82.4%) were men and 162 (17.6%) women, with a wide age range. Concomitant drug use were not reported in the Krupitsky and Grinenko (1997), Ocker et al. (2020), and Pradhan and Rossi (2020) studies. Concomitant drug use was reported in four studies (study # 4-5, 8, and 15), whereas one of them, the (Kolp et al., 2006), also stated that some of their participants had additional addictions and a range of different medicated mental disorders, without providing a complete dataset with participant characteristics. The 13 remaining studies did not include participants with concomitant drug use (study # 1-3, 9-14, 16, and 18-19).

Psychiatric comorbidities varied among the included studies. There was no mention of any psychiatric comorbidities in the Krupitsky et al. (1992), Ocker et al. (2020), and Pradhan and Rossi (2020), so it is unclear what kind of mental state these participants were in and whether there was any contraindicated disorders or medication. Out of the remaining 16 studies, four reported additional psychiatric disorders among their participants (study # 4, 8, 15 and 19). In the Grabski et al. (2022) study it was noted that the participants did not have any psychiatric comorbidities except for depression and anxiety, while it in the Sessa et al. (2021) study was reported that most of the patients had psychiatric comorbidities, and this was mainly depression and anxiety. It is therefore a possibility that participants in studies with no report of psychiatric comorbidities, potentially also has additional mental disorders, especially depression and anxiety, that has not been mentioned as it is more common than not with addiction.

Table 2: Participant diagnosis, diagnostic criteria, age and gender distribution, concomitant drug use, and psychiatric comorbidities.

#	Group	Diagnosis	Diagnostic criteria	Age	Gender distribution (male/female)	Concomitant drug use (yes/no)	Psychiatric comorbidities (yes/no)
1	Bogenschutz et al. 2015	AUD	DSM-IV for AUD	25-56	6/4	No	No
2	Dakwar et al. 2020	AUD	DSM-IV for AUD	Mean age 53.0±9.8	19/21	No	No
3	Das et al. 2019	High drinking levels	AUDIT scores 22.13±4.93	Mean age 27.48±8.11	55/35	No	No
4	Grabski et al. 2022	AUD	DSM-IV for AUD	Mean age 44.1±10.6	61/35	Yes	Yes
5	Kolp et al. 2006	AUD	DSM-IV for AUD	21-64	Not reported	Yes	No
6	Krupitsky and Grinenko 1997	Treatment-resistant, unable to maintain sobriety for a 3-month period, and several years of alcohol withdrawal symptoms	Not reported	Mean age 36.5±7 (active) and 38.4±0.81 (control)	211/0	Not reported	No
7	Krupitsky et al. 1992	Treatment-resistant, unable to maintain sobriety for a 3-month period, experienced withdrawal symptoms	Not reported	Mean age 33.4±1.07 (active) and 38.4±0.47 (control)	186/0	Not reported	Not reported
8	Sessa et al. 2021	AUD	DSM-IV for AUD	18-65	8/6	Yes	Yes
9	Dakwar et al. 2014	OUD	DSM-IV for OUD	Mean age 47.5±5.5	7/1	No	No

10	Dakwar et al. 2017	SUD	Active dependence with at least 8 days of use or 4 binges of large amounts over the past 30 days, and at least one positive utox during screening	Mean age 48.6±6.1	11/9	No	No
11	Dakwar et al. 2019	SUD	DSM-IV for SUD	Mean age 47.0±9.3	41/14	No	No
12	Jovaisa et al. 2006	OUD	DSM-IV or ICD-10 for OUD	Mean age 22.7±3.0 (active) and 23.4±3.1 (control)	43/7	No	No
13	Krupitsky et al. 2002	OUD	DSM-IV or ICD-10 for OUD	Mean age 23.0±4.4 (active) and 21.6±3.0 (control)	55/15	No	No
14	Krupitsky et al. 2007	OUD	DSM-IV or ICD-10 for OUD	18-35	49/10	No	No
15	Lalanne et al. 2016	Opioid-induced hyperalgesia and chronic lumbar pain	DSM-IV for OUD	36	0/1	Yes	Yes
16	Ocker et al. 2020	Opioid-induced hyperalgesia and CRPS-I	Not reported	55	1/0	No	Not reported
17	Pradhan and Rossi 2020	OUD	Not reported	Not reported	Not reported	Not reported	Not reported
18	Azhari et al. 2021	CUD	DSM-IV for CUD	Mean age 42.5±13.5	4/4	No	No
19	Johnson and Black 2020	SUD, CUD	DSM-IV for SUD, CUD and MDD	22	1/0	No	Yes

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition; AUD: Alcohol use disorder; AUDIT: Alcohol use disorder identification test; OUD: Opioid use disorder; SUD: Stimulant use disorder; ICD-10: International Classification of Diseases 10th edition; CRPS-I: Complex regional pain syndrome type 1; CUD: Cannabis use disorder; MDD: Major depressive disorder.

Treatment models and objectives

Table 3 summarizes the different combinations of treatment interventions and tools used in the included studies for treating the different addictions.

Two studies did not use any form of therapy, mindfulness exercises, counseling, education, or rehabilitation prior to, during, or after the psychedelic treatments (Dakwar et al., 2017; Lalanne et al., 2016). The remaining studies utilized some sort of therapeutic practice in their treatment models, either alone or in combination with other treatments. Nine studies used

psychotherapy (ref. Table 3), one cognitive behavioral therapy (Ocker et al., 2020), three motivational enhancement therapy (Azhari et al., 2021; Bogenschutz et al., 2015; Dakwar et al., 2020), three mindfulness-based relapse prevention (Azhari et al., 2021; Dakwar et al., 2019; Grabski et al., 2022), one alcohol education (Grabski et al., 2022), and one addiction counseling (Krupitsky et al., 2007). One study offered mandatory aftercare programs, either abstinence-based, outpatient counseling, or residential rehabilitation programs (Jovaisa et al., 2006), one used TIMBER in combination with rTMS (Pradhan & Rossi, 2020), and one study used relaxation and mindfulness exercises in combination with aversion therapy (Krupitsky & Grinenko, 1997).

Some studies used combinations of the methods mentioned above, e.g., motivational enhancement therapy with psychotherapy (Bogenschutz et al., 2015), mindfulness-based relapse prevention and alcohol education (Grabski et al., 2022), and psychotherapy with aversion therapy (Krupitsky & Grinenko, 1997).

Follow-up length varied greatly among the included studies, and the Azhari et al. (2021), Pradhan and Rossi (2020), and Lalanne et al. (2016) studies did not include a period for follow-up after the treatments. The Dakwar et al. (2017) had a noticeable short follow-up length of only 2 weeks. The other ranged from one month to three years.

Table 3: Main purpose and treatment context for the included studies. Psychedelic substance and placebo substance/intervention with dose, administration and number of times administered, as well as follow-up length.

#	Group	Main purpose	Psychedelic substance	Placebo substance/ intervention	Treatment context	Follow-up length (months)
1	Bogenschutz et al. 2015	Assessment of the safety and efficacy of psilocybin in combination with MET for AUD, and improvement on study outcomes	**Psilocybin** Dose: **0.3-0.4 mg/kg** Administration: Oral Times administered: 2	No control	12-week treatment with **MET** and **PT**	9
2	Dakwar et al. 2020	Test whether a single ketamine infusion improves abstinence and time to relapse in patients with SUD engaging in MET-treatment	**Ketamine** Dose: **0.71 mg/kg** Administration: IV Infusion length: 50 min Bolus: Ketamine/saline, 2 min Times administered: 1	**Midazolam** Dose: **0.025 mg/kg** Administration: IV Infusion length: 50 min Bolus: Saline, 2 min Times administered: 1	5-week outpatient treatment with **MET**	6
3	Das et al. 2019	Assessment of ketamine for MRM RET in harmful drinkers, reducing the reinforcing effects of alcohol and long-term drinking levels	**Ketamine** (RET+KET) Dose: **350 ng/dl** Administration: IV Infusion length: 30 min Times administered: 1 **Ketamine** (NO RET+KET) Dose: **350 ng/dl** Administration: IV	**Saline** (RET+PBO) Administration: Intravenous Infusion length: 30 min Times administered: 1	9-month treatment with **PT** and **MRM retrieval**	9

			Infusion length: 30 min Times administered: 1			
4	Grabski et al. 2022	Investigate the safety and efficacy of ketamine compared to placebo in increasing abstinence in patients with AUD, and pilot ketamine in combination with either MBRP or AE	**Ketamine** with therapy Dose: **0.8 mg/kg** Administration: IV Infusion length: 40 min Times administered: 3 **Ketamine** with AE Dose: **0.8 mg/kg** Administration: IV Infusion length: 40 min Times administered: 3	**Saline** with therapy Dose**: 0.9 %** Administration: IV Infusion length: 40 min Times administered: 3 **Saline** with AE Dose: **0.9 %** Administration: IV Infusion length: 40 min Times administered: 3	10-visit treatment with **MBRP** and **AE**	6
5	Kolp et al. 2006	Assess whether ketamine-enhanced psychotherapy can increase abstinence rates among patients with AUD	Dose is not reported, but "the Krupitsky et al. (1992) study was used as a benchmark to guide Kolp`s work". **Ketamine** in 5 different treatment methods (double session for method 5/5) Dose: **3.0 mg/kg** Administration: IM Times administered: 1-2	No control	Five different treatment models with daily or weekly **PT**	12
6	Krupitsky and Grinenko 1997	*To assess the efficacy of Ketamine-psychotherapy in abstinence, compared to traditional treatment of AUD*	**Ketamine** Dose: **2.5 mg/kg** Administration: IM Treatment length: 45-60 min Times administered: 1	Conventional pharmacological and therapeutic treatment of AUD	3-month treatment comprising of 3 phases with **PT** and **AT**	12, 24, and 36
7	Krupitsky et al. 1992	To assess the efficacy of the Affective Contra-Attribution (ACA) method in degree of abstinence, compared to traditional treatment of AUD	**Ketamine** Dose: **3.0 mg/kg** Administration: IM Times administered: 1	Conventional pharmacological and therapeutic treatment of AUD; aversive emetic therapy, pharmacological treatment of craving, and individual and group therapy	Treatment comprising of 3 phases with **PT** and **AT**	12
8	Sessa et al. 2021	Assess if MDMA-assisted psychotherapy can be delivered safely and be tolerated by patients with AUD, as well as improve study outcomes related to abstinence and quality of life	**MDMA** Dose: **25 mg + 62.5 mg** Administration: Oral Times administered: 2	No control	10-week treatment with **PT**	9
9	Dakwar et al. 2014	Assess the effects of ketamine on SUD[2], the tolerability of two doses and how they affect cue-induced craving and motivation to quit	**Ketamine (K1)** Dose: **0.41 mg/kg** Administration: IV Infusion length: 52 min Times administered: 1 **Ketamine (K2)** Dose: **0.71 mg/kg** Administration: IV	**Lorazepam (LZD)** Dose: **2.0 mg** Administration: IV Infusion length: 52 min Times administered: 1	9-day treatment with **relaxation** and **mindfulness-based exercises**	1

			Infusion length: 52 min Times administered: 1			
10	Dakwar et al. 2017	To detect behavioral shifts in the relative salience of cocaine now vs. money later, longer than 24 hours post-infusion	**Saline** Administration: IV Infusion length: 50 min Bolus: Saline, 2 min Times administered: 1 **Ketamine** Dose: **0.60 mg/kg** Administration: IV Infusion length: 50 min Bolus: 0.11 mg/kg ketamine/saline, 2 min Times administered: 2	**Saline** Administration: IV Infusion length: 50 min Bolus: Saline, 2 min Times administered: 1 **Midazolam** Dose: **0.025 mg/kg** Administration: IV Infusion length: 50 min Bolus: Saline, 2 min Times administered: 2	Three 6-day treatments with **verbal choice procedures** for self-administration of cocaine.	2 weeks
11	Dakwar et al. 2019	Test whether a single ketamine infusion improves abstinence and time to relapse in patients with SUD[2] engaging in MBRP-treatment	**Ketamine** (n=27) Dose: **0.5 mg/kg** Administration: IV Times administered: 1	**Midazolam** (n=28) Dose: **0.025 mg/kg** Administration: IV Times administered: 1	5-day treatment with **MBRP** and **behavioral treatment**, with additional outpatient **MBRP** during follow-up	6
12	Jovaisa et al. 2006	Evaluate the effect of subanesthetic ketamine infusion for suppressing opiate withdrawal symptoms; the long-term effects; subsequently, abstinence and post-infusion treatment retention	**Ketamine** Dose: **0.5 mg/kg/h** Administration: IV Times administered: 1	**Saline** Administration: IV Times administered: 1	5-day inpatient **OT** under **GA** with mandatory aftercare plan (**abstinence-based**, **counseling** or **rehabilitation**)	4
13	Krupitsky et al. 2002	To assess the safety and efficacy of KPT for patients with OUD, using one high-dose and one low-dose group to compare psychedelic experience, abstinence, craving, and positive change in nonverbal unconscious emotional attitudes	**Ketamine** Dose: **2.0 mg/kg** Administration: IM Treatment length: 1.5-2 hrs Times administered: 1	**Ketamine** Dose: **0.2 mg/kg** Administration: IM Treatment length: 1.5-2 hrs Times administered: 1	5-day treatment with **PT**	24
14	Krupitsky et al. 2007	Assessing the efficacy of single vs. repeated session ketamine-assisted PT for abstinence, reduction in craving and positive change in nonverbal unconscious emotional attitudes	**Ketamine** Dose: **2.0 mg/kg** Administration: IM Treatment length: 1.5-2 hrs Times administered: 3	**Ketamine** Dose: **2.0 mg/kg** Administration: IM Treatment length: 1.5-2 hrs Times administered: 1	3-month treatment with **PT** and **AC**	12
15	Lalanne et al. 2016	To test opioid tapering using oral ketamine to reduce withdrawal symptoms and	**Ketamine** Dose: **1.0 mg/kg** (5.0 mg/ml) Administration: Oral Times administered: 1	No control	Gradual, monitored **OT**	No follow-up

		successfully reduce the need for opioids				
16	Ocker et al. 2020	Test whether a multimodal, integrated ketamine-approach can promote successful opioid tapering, reduce pain, withdrawal symptoms and promote long-term abstinence	**Ketamine** Dose: **0.09-0.6 mg/kg** Administration: IV Times administered: 5-day continuous infusions **Ketamine** Dose: Up to **0.77 mg/kg** Administration: IV Times administered: 5-days continuous infusions	No control	Two 5-day continuous treatments with **OT** and **CBT**, with additional **CBT** during follow-up	12
17	Pradhan and Rossi 2020	To test the feasibility and efficacy of ketamine, rTMS, and TIMBER in patients with OUD	**Ketamine** Dose: **0.75 mg/kg** Administration: IV Infusion length: 45 min (stopped at 745 mg total) Times administered: 1	No control	**rTMS** and **TIMBER**	No follow-up
18	Azhari et al. 2021	Assess the impact of ketamine in combination with MET and MBRP on motivation to quit, reduce cravings and promote abstinence	**Ketamine** (ADM1) Dose: **0.6 mg/kg** Administration: IV Infusion length: 50 min Bolus: 0.11 mg/kg ketamine/saline, 2 min Times administered: 1 **Ketamine** (ADM2) Dose: **0.6 mg/kg** Administration: IV Infusion length: 90 min Bolus: 0.11 mg/kg ketamine/saline, 2 min Times administered: 1	No control	6-week outpatient treatment with **MET** and **MBRP**	No follow-up
19	Johnson and Black 2020	Explore the therapeutic potential of classic psychedelics in assisting with treatment of SUD (with co-occurring depression)	**LSD** Dose: **200-500 mcg** Administration: Oral Times administered: 5 ***DMT*** *Dose: **50-100 mg*** *Administration: Inhalation* *Times administered: 4*	No control	Continuous **PT** over several years, with participation in relapse-prevention program	8

AC: Addiction counseling; AE: Alcohol education; AT: Aversion therapy; AUD: Alcohol use disorder; AWS: Alcohol withdrawal symptoms; CBT: Cognitive behavioral therapy; GA: General anesthesia; IM: Intramuscular; IV: Intravenous; KPT: Ketamine psychotherapy; MBRP: Mindfulness-based relapse prevention; MET: Motivational enhancement therapy; MRM: Maladaptive reward memories; OT: Opioid tapering; OUD: Opioid use disorder; PT: Psychotherapy; RET: MRM retrieval during "reconsolidation window"; SUD: Stimulant use disorder.

Study outcomes

The study outcomes for the measurements abstinence and changes in craving are summarized in Table 4, as well as report of any adverse event during the treatments.

Adverse events were not reported in the Krupitsky and Grinenko (1997) and Johnson and Black (2020), while the other studies provided a short summary of the events and most did not publish complete data of any such events.

Table 4: Study outcomes for the included studies; abstinence and craving. Report of any adverse events during treatments.

#	Group	Abstinence	Craving	Adverse events (yes/no)
1	Bogenschutz et al. 2015	Significant decrease in use up to 36 weeks post treatment	From baseline mean 16.0 vs. 9-month mean 8.11 (using PACS)	Yes
2	Dakwar et al. 2020	52.9% abstinence across the 21 days post-infusion, compared to 40.9% in control	*Not reported*	Yes
3	Das et al. 2019	Significant reduction in total alcohol consumption (from baseline to 9-month follow-up) for RET+KET (23.5 UK units), some for NO RET+KET (13.6 UK units), and no for RET+PBO (4.9 UK units). Long-term reduction with no evidence of rebound. RET+KET halved their weekly consumption (84-41 UK units)	Significant reduction in reactivity (day 1 vs. day 10) in RET+KET, not in control groups	Yes
4	Grabski et al. 2022	86.5% abstinence at 6 months in ketamine-therapy group, 82.5% in ketamine-AE, 78.3% in placebo-therapy, and 70.7% in the placebo-AE group (mean difference 10.1)	No significant reduction in alcohol craving (using ACQ-NOW)	Yes
5	Kolp et al. 2006	Approximate 1-year abstinence for group 1-5: 25% vs. 35% vs. 50% vs. 60% vs. 70%	*Not reported*	No
6	Krupitsky and Grinenko 1997	65.8% abstinence at 12 months compared to 24% in control	*Not reported*	Not reported
7	Krupitsky et al. 1992	69.8% abstinence at study end (1 year) compared to 24% in control	*Not reported*	No
8	Sessa et al. 2021	Complete abstinence in 64% at 9-months. From 130.6 units/week to 0.0 at baseline and during treatment. Steady increase in consumption to 6-month follow-up, and a reduction to 18.7 units/week at 9-months	*Not reported*	No
9	Dakwar et al. 2014	50% 2-week abstinence. Significant reduction in cocaine use (baseline: 22/28 days/use vs. follow-up: 5/28 days/use)	Significant decreased craving scores in K1 relative to LZP (median 65 vs. -126) and K1 relative to LZP (median 53 vs. -18) (using VAS-C)	Yes
10	Dakwar et al. 2017	67% reduction in self-administration of cocaine from baseline to 28-hours post-infusion, compared to 10% in control	Significant reduction (ca. 60%) compared to (ca. 15%) control. This was not sustained throughout the monitoring period (VAS-C)	Yes
11	Dakwar et al. 2019	48.2% abstinence at 5 weeks compared to 10.7% in control	Craving rated 58.1% lower in ketamine-group than in control group. No evidence of change over time in both groups) (VAS-C)	Yes
12	Jovaisa et al. 2006	18% abstinence at 4-month follow-up compared to 15% in control	*Not reported*	No
13	Krupitsky et al. 2002	Significant difference in abstinence between groups at 14/16 time points over 24 months, with much greater abstinence in high-dose group. 50% went back to using within the 3 first months, compared to 60% in control	Significant reduction from pre-treatment to post-treatment in both groups. 29.24 to 1.71 in high-dose group vs. 36.34 to 0.00 (n=1) in low-dose group (using VAS-C)	Yes
14	Krupitsky et al. 2007	50% 1-year abstinence compared to 22.2% in control	Significant reduction from baseline to 12 months, 20.1±4.7 to 0.3±0.2 in	Yes

			multiple session group vs. 22.8±5.4 to 0.0±0.0 in control (using VAS-C)	
15	Lalanne et al. 2016	Dramatically reduced doses of opioid painkillers. Ketamine withdrawn without any withdrawal symptoms	No measurement for comparison were reported, other than significant craving before treatment vs. no cravings to report after treatment	Yes
16	Ocker et al. 2020	Complete abstinence throughout treatment period and 1-year follow-up	*Not reported*	Yes
17	Pradhan and Rossi 2020	*Not reported*	Baseline 23.66 reduced to 8.33 post-treatment. 65.7% decrease in craving (using OCS)	No
18	Azhari et al. 2021	75% abstinence for at least 3 weeks. Significant reduction in using days/week (baseline: 5.1 vs. post-infusion: 0.8 vs. study end: 0.5)	Significant difference in craving between baseline and study end (using VAS-C)	No
19	Johnson and Black 2020	3-year abstinence from stimulants. Reduction in cannabis consumption from daily to weekly use. Clear reduction in times used and more than 50% reduced dose of recreational psychedelics	*Not reported*	Not reported

Note. ACQ-NOW: Alcohol Craving Questionnaire; OCS: Opiate Craving Scale; PACS: Penn Alcohol Craving Scale; VAS-C: Visual Analog Scale – Craving

Abstinence and craving

Except for the Pradhan and Rossi (2020) study, all the included studies had measures for abstinence. This measurement varied widely from as low as 18% in the Jovaisa et al. (2006) study to 86.5% in the Grabski et al. (2022) study, or even complete abstinence throughout the follow-up period as reported in the case report by Ocker et al. (2020). Seeing as the empirical clinical observations by Kolp et al. (2006) were based on five different treatment models, the outcome from these treatments also varies greatly from 25% to 70% abstinence rate. All controlled studies showed distinction between active group and control group to some extent, even as big a difference as reported in the Dakwar et al. (2017) study, with 67% vs. 10% reduction in self-administration. Apart from this, there does not seem to be differences in abstinence rates based on addiction type, psychedelic substance, treatment context, or applied interventions.

Changes in craving was not measured in eight of the included studies (study # 2, 5-8, 12, 16, and 19). For the remaining studies, all reported significant reduction in craving except for the Grabski et al. (2022) study, who reported no significant reduction. In the controlled studies, we see a noticeable smaller reduction in craving between active and control in those using low-dose versus high-dose psychedelic substances (Krupitsky et al., 2002), and multiple sessions versus single session with psychedelic substances (Krupitsky et al., 2007), compared

to those using comparably more different control substances or interventions (Dakwar et al., 2017; Dakwar et al., 2019).

Depression and anxiety

Several studies have reported beneficial effect from the psychedelic experiences in relation to depression and anxiety (Azhari et al., 2021; Bogenschutz et al., 2015; Dakwar et al., 2014; Grabski et al., 2022; Johnson & Black, 2020; Krupitsky et al., 2002; Sessa et al., 2021). Reduced anxiety, depression, and symptoms of anhedonia was reported by Krupitsky et al. (2002) – with no significant difference between high-dose and low-dose group. They also measured improvements in several categories of nonverbal unconscious emotional attitudes related to self-image, motivation, hopes, and connection to others – which in turn are reported to be important tools in managing depression and anxiety (Krupitsky et al., 2002). It`s worth mentioning that this decrease in depression was not sustained over time as reported in some studies with substantial follow-up (Bogenschutz et al., 2015; Sessa et al., 2021).

Discussion

The purpose of this review was to identify and map published studies treating addiction with pre-selected psychedelic substances, in a therapeutic or clinical context with a behavioral outcome or therapeutic gain. Subsequently, identify limitations and knowledge gaps with the conducted research to inform future research and actions. Only 13 studies were identified with the limitation of being performed in a therapeutic context, and six additional studies were identified after including clinical studies with a behavioral outcome or therapeutic gain. This resulted in fewer studies than first anticipated, especially studies utilizing the classic psychedelic substances and MDMA. Therefore, it would be too early to make any assumptions about their implication and effectiveness in addiction treatments. However, these studies serve as a good foundation for future research. To our surprise, much research was performed with ketamine, both in combination with therapy or behavioral interventions, and as a general anesthesia under detoxification to reduce withdrawal symptoms. Since ketamine is classified as a schedule III substance, and available through prescription, it is easier to obtain and utilize for research than for instance MDMA, which still is classified as a schedule I substance with “breakthrough therapy” status granted by the FDA (Kolp et al., 2014; Perkins et al., 2021). The amount of ketamine research identified for this review (16 of the 19

included studies) does however provide quite a substantial amount of data to evaluate ketamine`s potential in addiction treatment, although there are notably great methodological differences between the included studies.

There is inconsistent reporting of outcomes for abstinence and changes in craving. Both are important factors when evaluating long-term effect from treatment, and reduced craving is an essential factor in obtaining and maintaining abstinence. Abstinence was not reported in the Pradhan and Rossi (2020) study, as they measured changes in craving and increase in mindfulness as their outcomes for evaluating the efficacy and feasibility of their treatment combination of ketamine, rTMS, and TIMBER. Craving decreased by 65.7% (Pradhan & Rossi, 2020), which is impressive and indicates some form of change for the participant, but it does not say anything about whether these participants managed to stop using opioids, if even for a short period of time. For the remaining 18 studies, abstinence ranged from 18% to 86.5%, where some of the lowest scores were reported in ketamine-studies (Jovaisa et al., 2006; Kolp et al., 2006; Krupitsky et al., 2002). Apart from 11 ketamine-studies utilizing some form of control substance or intervention, the remaining studies were all un-controlled. But because the controls used are significantly dissimilar, it is impossible to say how much this affects abstinence outcomes, through for instance, less motivation to quit. It is also worth mentioning that abstinence has been measured differently and under dissimilar circumstances. Consistent reporting of these outcomes would lead to better comparison amongst interventions. Abstinence rates might fluctuate some in the time after treatments before stabilizing, which follow-up can confirm and in parts explain.

Craving was measured in 11 of the included studies, where all reported significant reduction except for the Grabski et al. (2021) study. Even though there are no apparent patterns between abstinence and craving outcomes based on administration route or dosage of psychedelic substance, this is most likely affected by methodological differences. A full psychedelic experience is associated with higher abstinence rates (Krupitsky et al. 2002), at least theoretically indicating greater results in studies with higher doses of psychedelic substances. Krupitsky et al. (2002) demonstrated the difference in abstinence and craving in a low dose versus high-dose ketamine trial, resulting in significant difference in abstinence between groups and significantly reduced craving in both groups. In the Krupitsky et al. (2007) study they also evaluated abstinence and craving in single session versus multiple session ketamine groups, reporting significantly higher outcomes in the multiple session group. It is unclear whether the most effective way to go is through multiple sessions, high-dose treatments, or maybe through a combination of the two. It is regardless implication for further trials

investigating dosage, administration route, and the number of sessions needed to maximize treatment outcomes.

To summarize, there are both similarities and dissimilarities in measured abstinence and changes in craving for the included studies. There are also methodological differences and inconsistencies in applied treatments among participants, that might to some extent contribute to these differences. With the current research, it is difficult to understand which treatment leads to what effect and whether there is possible synergy between the intervention and psychedelic substances. The possibility of synergy has been discussed by many, but most conclude that more research is needed to establish evidence of this (Das et al. 2019; Bogenschutz et al. 2015; Sessa et al. 2021; Dakwar et al. 2019). The figurative psychological landscape created by the psychedelic substance should indicate the need for the right tools to navigate said landscape correctly, and to achieve behavioral change. The patient is more susceptible to change while under the influence of psychedelic substances, but it is impossible to say how easy or challenging it is to achieve positive change without guidance. Still, the possibility of synergy is an exciting and important prospect to investigate further, where a more suitable study design should allow for measurement between the psychedelic treatment and the behavioral intervention. A suggestion is to include more than one control group, for example by including one active control group receiving only the behavioral intervention, and one control group receiving only the psychedelic intervention.

As mentioned previously, there is a noticeable amount of critique of the psychedelic research performed prior to the prohibition, which have been addressed in several articles (Krebs & Johansen, 2012; Nigam & Pandurangi, 2021; Rucker et al., 2018). The introduction of certain guidelines, standards, and strategies for psychedelic research have the potential to increase the safety of everyone involved in the treatments, address methodological flaws, and ensure transparent research. The level of details provided for the publicly available material for all the included studies varies greatly, which in turn makes it difficult to replicate the studies and build on their progress (Petranker et al., 2020). Petranker et al. (2020) highlighted pre-registration of the trials prior to its execution, with analysis plan and treatment protocol, as well as making all data and material available and published. Our extensive search could only find that three of the included studies have provided this (Azhari et al., 2021; Dakwar et al., 2020; Grabski et al., 2022).

An example of limited available information is the lack of reported ketamine-dose administered in the Kolp et al. (2006) study, which also makes it difficult to evaluate optimal dose for future trials. More severe though, is the inconsistency in reporting of any adverse

effects, which have been previously documented to be a liable risk associated with these substances (Rucker et al., 2018). By reporting these effects, researchers can better predict and prepare for anything that could happen during the treatments, and to some extent prevent them from happening. This limitation is therefore something that should be avoided in future research, and perhaps will be less evident in some of the ongoing multisite psychedelic research funded by MAPS (MAPS, 2022). This cooperation between countries can connect researchers and provide a platform for communication and transparency.

Psychiatric comorbidities and concomitant drug use were inconsistently reported in the included studies. The safety-guidelines proposed by Johnson and affiliates (2008) emphasizes the importance of safety-related selection criteria, especially contraindicated psychosocial function, which can be identified through psychological screening, and concomitant drug use. Some mental disorders such as schizophrenia, psychotic disorders, and bipolar disorder are contraindicated in psychedelic studies, as their reaction to the experience can be volatile and unpredictable (Johnson et al. 2008). Additional medication could possibly alter the effects from the psychedelic substances, both increase and decrease their effect as well as interact and create new and unpredictable reactions. There is not enough information about how different medications or mental disorders could affect the psychedelic experience or the outcomes from the treatments. We therefore do not know whether the results could be contributed by the additional medication, or if perhaps the presence of certain mental health disorders in combination with addiction decreases the effects from the treatments.

Several of the included studies also have reports of patients with additional depression and/or anxiety that have benefited profoundly from the psychedelic treatments. The characteristics and functionality of the substances` antidepressant effects are still not completely understood, as is their role in treating addiction. It is not uncommon for addicts to also struggle with depression and anxiety, or other more severe mental disorders. But then it is also important to clearly define and report these participant characteristics and qualities, as we do not know what kind of impact the absence or presence of these additional diagnosis` might have on the treatment outcomes, or whether any findings can be extended to the general population (Petranker et al. 2020). Variations within the same treatment groups could perhaps to some extent be contributed by dissimilarities in participant characteristics, seen in groups where some have additional psychiatric comorbidities, and some do not. Heterogenous groups where, for instance, some of the participants have psychiatric comorbidities while the rest do not, is something to avoid (if possible) when implementing psychedelic-assisted addiction research.

Inconsistencies when defining the treatment groups have also been accentuated by Rucker et al. (2017), and how it can even result in selection bias. It's important to remember that participants might present with different levels of motivation and adherence to the treatments based on mental, physical, and social factors, for instance, additional psychological disorders, not to mention individual and unexpected reactions from the psychedelic substances. Lack of randomization and blinding between active and control groups can potentially introduce bias, since the group receiving the psychedelic treatment might present with more motivation to obtain and maintain abstinence than the control group, as is mentioned as a possibility in the Krupitsky et al. (1992) study. Whether the patients are treatment-seeking and have a diagnosis or not can also impact their motivation to maintain abstinence, as those who have acknowledged their disorder and are actively trying to change have perhaps come a longer way and are more motivated than those who have not progressed so far as to see the need or want to change. Such bias can also be present when there are great differences in participant characteristics within the same group, for instance, groups containing participants who uses different medications or have different mental states, as is seen in most of the included studies.

Conclusion

This review highlighted the current research status for psychedelic-assisted addiction treatments. Little research has been conducted with the classic psychedelics and MDMA, but there is comprehensive research into ketamine`s potential in addiction treatments.
Moving forward, consistency in outcomes and methodological rigor should be emphasized, with a substantial follow-up period to identify trends and long-term treatment maintenance. The synergy aspect can be further investigated by introducing more than one control group, and should be strengthened with randomization and participants with homogenous characteristics. Future research should take into account the published checklist, guideline, and strategy presented in this review, which addresses limitations with the research conducted prior to the psychedelic prohibition.

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Appendix 1: Keywords and terms

Appendix I: Keywords and terms collected before, during and after the preliminary search, used to build the comprehensive search strategy.	
Psychedelics	• Psychoactive/psychotropic/psychotogenic/psychotomimetic (substance*) • Hallucinogen* • Entactogen/empathogen • LSD "Lysergic acid diethylamide" • Lucy, "acid", "lsd-25" • Psilocybin • Magic mushroom, "shrooms" • MDMA "N-Methyl-3,4-methylenedioxyamphetamine"/ "3,4-methylenedioxymethemphetamine" • Molly, "ecstasy", xtc, "E" • Ketamine hydrochloride "2-(2-chlorophenyl)-2-(methylamino)cyclohexanone" • Ketamine, "Kit kat", "special K, "k", "ket", calypsol • Psychedelic agent* • Psychotogenic/Psychotomimetic (substance*) • Entactogen*
Addiction	• Addict* • Alcohol* • Substance/alcohol/narcotic related disorder* • Drug dependence • Substance related disorder* • Dependency • Substance abuse • Misuse
Psychotherapy	• Psychotherapy • Therapy • Treatment* • Psychiatric treatment* • Research • Medical research • Experimental research • Psychedelic-assisted • Rehabilitation • Psychosocial intervention* • Psychopharmacotherapy • Substance assisted treatment
Extra	• History • Mental health • Public health • Safety • Protocol* • Guideline* • Study* • Trial* • Clinical trial* • Norway • Psychedelic Harm Reduction and Integration "PHRI"

Appendix 2: First proposed search strategy

Appendix 2: The first proposed search strategy. This was used together with keywords and terms from the list in Appendix 1 to create the search strategy utilized January 29th (the first comprehensive search".	
Search	**Query**
#1	mdma *OR* 3,4-metylendioksy methamphetamine *OR* ecstasy *OR* molly
#2	lsd *OR* lysergic acid diethylamide *OR* acid *OR* lucy
#3	psilocybin *OR* magic mushroom* *OR* shroom*
#4	ketamine *OR* special k *OR* kit kat
#5	psychedelic* *OR* hallucinogen* *OR* psychoactive *OR* psychotogenic *OR* psychotomimetic *OR* entactogen
#6	trial* *OR* clinical trial*
#7	psychotherapy *OR* therapy *OR* rehabilitation *OR* treatment* *OR* psychosocial intervention*
#8	protocol* *OR* guideline* *OR* phri
#9	addict* *OR* alcohol* *OR* substance abuse *OR* drug dependence *OR* alcohol dependence
#10	#1 *OR* #2 *OR* #3 *OR* #4
#11	#10 *AND* #5 *AND* #6 *AND* #7 *AND* #8 *AND* #9

Appendix 3: Proposed data charting tool for pilot testing

Appendix 3: Proposed data charting tool for pilot testing. "First author (year)" changed to "group" and "treatment/intervention" changed to "timeline for treatment/intervention". "Practice guidelines" and "study protocol" was removed, while "trial identification", "diagnosis (with diagnostic criteria", "concomitant drug use", "psychiatric comorbidities", "purpose", "pre-registration (analysis plan and/or study protocol", "study measures", and "additional relevant information" was added. Under "population", gender distribution "male/female" and "age" were added.

First author (year)	**Source**	**Study period**	**Study location**	**Population**	**Type of addiction**	**Behavioral outcome**	**Treatment/ intervention**
Substance and dose	**Practice guidelines**	**Study protocol**	**Study design**	**Primary outcome**	**Secondary outcome**	**Authors conclusions, interpretation, and recommendations**	

Appendix 4: Data collection

Complete data collection of all the 19 included studies using the self-made data charting tool.

Group	**Bogenschutz et al. 2015**
Source	*Journal of Psychopharmacology*
Trial identification	NCT01534494
Study period	January 2012 – March 2014
Study location	USA University of New Mexico Health Sciences Center, Albuquerque, New Mexico.

Type of addiction	Alcoholism
Population, n (male/female) Age	n=10/9 (6/4) Age 25-56
Diagnosis (Criteria for diagnosis)	AUD (DSM-IV for AUD)
Concomitant drug use	No
Psychiatric comorbidities	No
Study design	Open label, proof of concept study
Purpose	*Assessment of the safety and efficacy of psilocybin in combination with MET for AUD, and improvement on study outcomes.*
Psychedelic substance	Psilocybin Dose: 0.3-0.4 mg/kg Administration: Oral Times administered: 2
Control substance	No control
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	Yes
Study measures	*Questionnaires/ rating scales (CIWA-Ar, HRS, 5D-ASC, MEQ, ARCI, SIP, SOCRATES 8A, AASE, PACS, POMS) *Breath alcohol concentration (BAC) *Timeline Follow Back (TLFB) *Utox *Health check
Behavioral outcome	Acute and persisting effects of psilocybin in the context of outpatient alcoholism treatment – reduction in heavy drinking days.
Timeline for treatment/ intervention	12-week, 14-session manualized psychosocial intervention for alcoholism with psilocybin. *7 MET sessions (Motivational Enhancement Therapy). *3 preparation sessions. *2 debriefing sessions. *2 psilocybin sessions; participants completed questionnaires, assessments, a brief clinical interview, including mental status exam, 7 hours after drug administration. *4 sessions before the first psilocybin-session and 4 sessions between the two sessions. *Team of 2 therapists. *No control groups. *Assessments were done week 1-12 (treatment period), at week 24 and 36 (9-month follow-up).
Primary outcome(s)	*Changes in % heavy drinking days (baseline vs. week 5-12): Mean difference (SD)=26.0, p=0.008). *Changes in % drinking days (baseline vs. week 5-12): Mean difference (SD)=27.2, p=0.009). *Acute effects of psilocybin: Variable results, but some difference between session 1 and 2.
Secondary outcome(s)	*Motivation (using SOCRATES 8A): Significant improvement in (most) areas. *Self-efficacy to abstain from drinking (AASE): Significant improvement. *Craving (PACS): baseline Mean 16.00 vs. week 36 Mean 8.11. *Mood assessment (POMS): Significant improvement in (most) areas. *Adverse events: Headache (n=5), nausea (n=1), diarrhea (n=1), and insomnia (n=1).
Additional relevant information	*10 completed first psilocybin-session – included in analysis of first session acute effects. *7 completed second psilocybin-session (n=6 received dose 0.4 mg/kg). *9 completed all follow-up assessments - included in analysis of drinking outcomes.

Author conclusions, interpretations, and recommendations	*Highly variable subjective responses indicate need for high-dose treatments for alcoholics. *Some alcoholics are insensitive to psilocybin`s effects. *Participants exhibited significant improvement in drinking and significant changes in psychological measures relevant to drinking. *Much of the improvement occurred following psilocybin-administration.
Group	**Dakwar et al. 2020**
Source	The American Journal of Psychiatry
Trial identification	NCT02539511
Study period	September 2014 – September 2017
Study location	USA New York State Psychiatric Institute, Colombia University Medical Center campus
Type of addiction	Alcoholism
Population, n (male/female) Age	n=40 (19/21) Mean age 53.0±9.8
Diagnosis (Criteria for diagnosis)	AUD (DSM-IV for alcoholism with ≥4 heavy drinking days/past 7 days OR ≥35 (men) or ≥27 (women) weekly use)
Concomitant drug use	No
Psychiatric comorbidities	No
Study design	Triple-blinded, randomized controlled pilot trial
Purpose	Test whether a single ketamine infusion improves abstinence and time to relapse in patients with SUD engaging in MET-treatment
Psychedelic substance	Ketamine Dose: 0.71 mg/kg Administration: Intravenous Infusion length: 50 minutes Bolus: Ketamine/saline, 2 minutes Times administered: 1
Control substance	Midazolam Dose: 0.025 mg/kg Administration: Intravenous Infusion length: 50 minutes Bolus: Saline, 2 minutes Times administered: 1
Pre-registration (Analysis plan and/or study protocol)	Yes
Adverse events	Yes
Study measures	
Behavioral outcome	Promoted self-reported abstinence in alcoholics after ketamine vs. midazolam treatment
Timeline for treatment/ intervention	5-week outpatient ketamine-midazolam-assisted MET for alcoholism. *Week 1 with initial 1st MET-session (preparations, explore goals and motivations – counseling to reduce drinking days). *Week 2, 2nd session, a 52-minute intravenous infusion (2-minute bolus) of ketamine 0.11 mg/kg + 0.6 mg/kg (n=17) or midazolam 0.025 mg/kg (n=23). *Required to be abstinent for at least 24hrs pre-infusion. *Provided relaxation and mindfulness exercises before and during infusion. *Medical coverage 3hrs post-infusion (BP, HR, SPO_2). *Subjective-effects assessment after infusion. *Brief psychiatric evaluation before discharge. *Twice weekly MET-sessions at clinic, spaced by 3-4 days. *Provided with referrals after trial.

	*Telephone follow-up at 6-months.
Primary outcome(s)	*Alcohol abstinence (across the 21 days post-infusion): 52.9% (n=9/17) vs. 40.9% (n=9/22). *Proportions of alcohol abstinence (observed and model-estimated, across the 21 days post-infusion): Stable abstinence-rate in ketamine-group. Significant decrease in placebo-group over time. *Alcohol abstinence at 6-months (telephone interviews, 47.5% (n=19/40) response rate): 75% (n=6/8) in ketamine-group vs. 27% (n=3/11) in placebo-group.
Secondary outcome(s)	*% of participants with a heavy drinking day (across the 21 days post-infusion): 17.6% (n=3/17) in ketamine-group vs. 40.9% (n=9/22) in placebo-group. *Change in heavy drinking days (across the 21 days post-infusion): No significant change in ketamine-group (OR=0.98). Probability of heavy drinking days increased with each day following infusion for placebo-group (OR=1.19). *The two-way interaction of study week-by-treatment group was not significant in any of the models (craving, withdrawal, mindfulness, impulsivity, stress sensitivity, and self-efficacy). *Time to relapse (defined as first heavy drinking day or dropout across the 21 days post-infusion): 52.2% (n=12/23) in ketamine-group vs. 17.7% (n=3/17) in placebo-group. Ketamine-group had significantly longer time to relapse. No significant difference between groups in time to first use or to first heavy drinking day. *Drop-out: 0.0% (n=0/17) in ketamine-group vs. 26.1% (n=6/23) in placebo-group.
Additional relevant information	
Author conclusions, interpretations, and recommendations	*Ketamine effectively provided participants in MET greater odds of abstinence in the initial weeks after treatment. *Will a single ketamine infusion promote abstinence long term – single infusion versus multiple infusions for future research. *Is there synergy with behavioral treatments – investigate further. *Larger sample and longer follow-up.
Group	**Das et al. 2019**
Source	Nature Communications
Trial identification	ISRCTN10138262
Study period	June 2015 – November 2018
Study location	United Kingdom Clinical Psychopharmacology Unit, University College London Hospital, London.
Type of addiction	Alcoholism
Population, n (male/female) Age	n=90 (m=55) Age 27.48±8.11
Diagnosis (Criteria for diagnosis)	High drinking levels (Scoring >8 on AUDIT. Consuming >40 (men) or >30 (women) UK units/week)
Concomitant drug use	No
Psychiatric comorbidities	No
Study design	Single-blind, randomized controlled trial
Purpose	Assessment of ketamine for MRM RET in harmful drinkers, reducing the reinforcing effects of alcohol and long-term drinking levels.
Psychedelic substance	Ketamine (RET+KET) Dose: 350 ng/dl Administration: Intravenous Infusion length: 30 minutes Times administered: 1 Ketamine (NO RET+KET) Dose: 350 ng/dl Administration: Intravenous

	Infusion length: 30 minutes Times administered: 1
Control substance	Saline (RET+PBO) Administration: Intravenous Infusion length: 30 minutes Times administered: 1
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	Yes
Study measures	*Cue reactivity assessments *Questionnaires/ rating scales (BDI, BIS, BAS, DTS, PANAS, ACQ-NOW, SOCRATES 9, CEOA, OCDS, CADSS, BSS, DEQ, SHAPS) *Bloodwork *Gas chromatography
Behavioral outcome	Apparent reduction in alcohol consumption with no evidence of rebound.
Timeline for treatment/ intervention	9-month ketamine-assisted MRM (maladaptive reward memories) retrieval under psychotherapy for alcoholism. *3 face-to-face sessions and 4 remote (web-based or telephone) sessions. *1st session (baseline) to assess alcohol craving and mood. *2nd session with MRM retrieval and ketamine/placebo (day 3). *3rd session to assess effects of treatment (day 10). *Participants answered questionnaires to assess craving and mood, as well as blood-draws, blood pressure, gas chromatography and EEG. *Additional follow-up after two weeks, one, three, six and nine months.
Primary outcome(s)	(Day 1 vs. day 10) *Reactivity to sampled alcohol and alcohol cues (urge to drink, urge to drink more, anticipated enjoyment, actual enjoyment): Significant reduction in RET+KET, not for control. *Perceived changes in drinking levels: Significantly greater reduction for RET+KET. *Quantitative drinking days/weeks: Significant reduction for RET+KET (10.986), not for control (3.802). *Binges/week: Significant reduction for RET+KET, not for control. *Total alcohol consumption (via the Timeline Follow-Back, baseline to post-manipulation): Significant reduction for RET+KET (19.55, 23.5 UK units), some for NO RET+KET (6.527, 13.6 UK units), no for RET+PBO (0.726, 4.9 UK units).
Secondary outcome(s)	*Long-term maintenance (from baseline to 9-month follow-up): Reduction in all groups, with no evidence of rebound to baseline levels. RET+KET from ~84 to ~41 UK units. RET+KET (83%-40%) vs. NO RET+KET (65%-40%) vs. RET+PBO (68%-40%). *Predictive blood biomarkers of response (achieved blood plasma levels of ketamine during "reconsolidation window" predicts subsequent drinking): Moderate negative association between ketamine plasma levels and subsequent drinking in RET+KET (not for NO RET+KET).
Additional relevant information	
Author conclusions, interpretations, and recommendations	*The study highlights the promise of reconsolidated interference as a therapeutic mechanism in harmful drinking and offers key insight into the therapeutic application of ketamine. *Shows clear reduction in reinforcing effects of alcohol with ketamine.
Group	**Grabski et al. 2022**
Source	The American Journal of Psychiatry
Trial identification	NCT02649231
Study period	September 2016 – February 2020
Study location	UK

	NIHR Exeter Clinical Research Facility & NIHR University College London Hospitals Clinical Research Facility
Type of addiction	Alcoholism
Population, n (male/female) Age	n=96 (61/35) Mean age 44.1±10.6
Diagnosis (Criteria for diagnosis)	AUD (DSM-IV for AUD)
Concomitant drug use	Yes
Psychiatric comorbidities	Yes
Study design	Double-blind, randomized controlled phase II trial
Purpose	Investigate the safety and efficacy of ketamine compared to placebo in increasing abstinence in patients with AUD, and pilot ketamine in combination with either MBRP or AE
Psychedelic substance	Ketamine with therapy (KT) Dose: 0.8 mg/kg Administration: Intravenous Infusion length: 40 minutes Times administered: 3 Ketamine with AE (KA) Dose: 0.8 mg/kg Administration: Intravenous Infusion length: 40 minutes Times administered: 3
Control substance	Saline with therapy (PT) Dose: 0.9 % Administration: Intravenous Infusion length: 40 minutes Times administered: 3 Saline with AE (PA) Dose: 0.9 % Administration: Intravenous Infusion length: 40 minutes Times administered: 3
Pre-registration (Analysis plan and/or study protocol)	Yes
Adverse events	Yes
Study measures	*Questionnaires/ rating scales (BDI, HAM-D, SF-12, PSI, FTND, ACQ, VAS) *SCRAM bracelet alcohol monitoring systems *Bloodwork *Timeline Follow Back *Health check *Psychiatric assessment
Behavioral outcome	Reduced relapse rates and increased abstinence.
Timeline for treatment/ intervention	Ketamine-placebo-controlled, triple session treatment with MBRP and AE for alcoholics. *Visit 1 (screening) after telephone screening and detoxification to determine eligibility. *Visit 2, 4 & 6: 1.5h therapy/education session + 40min ketamine/placebo session. *Each infusion 1-3 weeks apart. *BP, HR and SPO_2 *Visit 3, 5 & 7: Therapy/education session 24-hours post-infusion.

	*Visit 8 is final therapy/education session. *Visit 9 for 3-month follow-up from visit 2. *Visit 10 for 6-month follow-up from visit 2.
Primary outcome(s)	*Self-reported days abstinent (at 6 months): 86.5 % KT 82.5 % KA 78.3 % PT 70.7 % PA Compares across therapy and education; mean difference=10.1 (95% CI=1.1, 19.0) *Alcohol relapse (at 6 months, defined as 1+ days of heavy alcohol use): 61.9 % KT 68.2 % KA 66.7 % PT 78.3 % PA No significant difference. Compared across therapy and education; odds ratio=0.7 (95% CI=0.28, 1.75)
Secondary outcome(s)	*Self-reported % days abstinent (at 3 months): Significant reduction compared to placebo. *Alcohol relapse (at 3 months, defined as 1+ days of heavy alcohol use): *Depressive symptoms (using BDI or HAM-D): Significant reduction in BDI compared to placebo at 3 months, but not at 9 months. Not significant at 3 and 6 month for HAM-D. *General health (using SF-12): No difference. *Psychotomimetic experiences (using the Psychotomimetic States Inventory): Significant reduction in anhedonia at 3 months. *Level of cigarette dependence (measured by the Fagerstöm Test for Nicotine Dependence): *Alcohol craving (using ACQ-NOW): No difference. *SCRAM bracelet alcohol readings: Positive correlation of SCRAM readings greater than 0 per participant between visit 2-8.
Additional relevant information	*Adverse events: 53 adverse events, where 4 were rated as severe. *Subjective drug effects (whether participants feel they received the active substance): After 1st infusion; 100% vs. 27%. After 2nd infusion: 95% vs. 34%. After 3rd infusion: 100% vs. 23%. *Blood sample analysis: Average ketamine blood levels were similar across all three infusions.
Author conclusions, interpretations, and recommendations	*Three ketamine infusions support abstinence from alcoholism. *Abstinence may be further enhanced in combination with therapy. *Treatment well tolerated. *A further definitive trial is warranted.
Group	**Kolp et al. 2006**
Source	The Humanistic Psychologist
Trial identification	Not identified
Study period	1996 – 1999
Study location	USA
Type of addiction	Alcoholism
Population, n (male/female) Age	n=70 (both males and females) Age 21-64
Diagnosis (Criteria for diagnosis)	AUD (DSM-IV for AUD)
Concomitant drug use	Yes

Psychiatric comorbidities	No
Study design	Empirical clinical observations
Purpose	Assess whether ketamine-enhanced psychotherapy can increase abstinence rates among patients with AUD
Psychedelic substance	Dose not reported, but noted that the Krupitsky et al. (1992) study was used as benchmark to guide this study: Ketamine in 5 different treatment methods (double session for method 5/5) Dose: 3.0 mg/kg Administration: Intramuscular Times administered: 1-2
Control substance	No control
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	No
Study measures	Not reported
Behavioral outcome	Abstinence from alcohol
Timeline for treatment/ intervention	#1: Individual outpatient treatment without residential component: *10 weekly, 50 minute sessions. *One ketamine administration. #2: Group intensive treatment with residential component. *30 hours of therapy weekly. *Daily sessions, all day. *One ketamine administration. #3: Group residential treatment with revised exclusion criteria. *30 hours of therapy weekly. *Daily sessions, all day. *Excluded participants with extensive history of psychedelic drug use. #4: Group residential treatment with revised exclusion criteria and increased intensity. *60 hours of therapy weekly. *Daily sessions, all day. *Increased two weeks and excluded participants with extensive history of psychedelic drug use. #5: Group residential treatment with revised exclusion criteria, repeated ketamine treatments and increased intensity. *90 hours of therapy weekly. *Daily sessions, all day. *Increased to three weeks, added second ketamine administration and excluded participants with extensive history of psychedelic drug use.
Primary outcome(s)	*1-year abstinence rate: 25% treatment #1 35% treatment #2 50% treatment #3 60% treatment #4 70% treatment #5
Secondary outcome(s)	
Additional relevant information	
Author conclusions, interpretations, and recommendations	*Results from the 5 different treatment models indicate that ketamine alone is not sufficient as a therapeutic agent, but in combination with therapy in a carefully crafted set and setting, does seem to show promise for treating alcoholism. *Authors speculate that ketamine has the potential to open certain “doors” for recovery, but that guidance is needed to access these doors (therapy with a licensed KEP-therapist). *Need for replication of this study with a larger sample and with control.

Group	Krupitsky and Grinenko 1997
Source	Journal of Psychoactive Drugs
Trial identification	Not identified
Study period	Not reported (4-year period?)
Study location	Russia (St. Petersburg) Leningrad Regional Center for Alcoholism and Drug Addiction Therapy
Type of addiction	Alcoholism
Population, n (male/female) **Age**	n=211 (211/0) Mean age 36.5±7 (active) and 38.4±0.81 (control)
Diagnosis (Criteria for diagnosis)	Treatment-resistant, unable to maintain sobriety for a 3-month period, and several years of alcohol withdrawal symptoms
Concomitant drug use	Not reported
Psychiatric comorbidities	No
Study design	Non-randomized clinical trial
Purpose	To assess the efficacy of Ketamine-psychotherapy in abstinence, compared to traditional treatment of alcohol dependency
Psychedelic substance	Ketamine Dose: 2.5 mg/kg Administration: Intramuscular Treatment length: 45-60 minutes Times administered: 1
Control substance	Conventional pharmacological and therapeutic treatment of AUD.
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	Not reported
Study measures	*Patient self-reporting *Questionnaires/ rating scales (MMPI, rating scale of negative experiences, LSI, LCS, PD, CTA, Kelly matrices, MVRG, MCRG QTLV, PLT, Spiritual scale) *Bloodwork *EEG
Behavioral outcome	Abstinence for at least 1 year (65.8% vs. 24%)
Timeline for treatment/ intervention	3-month KPT treatment course comprising of 3 stages for alcoholics. *3-month treatment with preparations is the 1st phase of therapy. *3-4-hours session with ketamine aimed at helping the patient find a new meaning and purpose to life, with a psychotherapist and a anesthesiologist. *Group therapy the day after ketamine-session, aimed at helping the patients make a correlation between the psychedelic experience and their intra- and interpersonal problems.
Primary outcome(s)	*1-year follow-up abstinence: 65.8% vs. 24%.
Secondary outcome(s)	*2-year follow-up abstinence: *3-year follow-up abstinence: *Influence of KPT on Personality (using MMPI, LSI, LCS): *Psychotomimetic changes (using PD and CTA): *Effect on Life Values (using QTLV): *Effect on understanding the meaning and purpose of one`s own life (using PLT): *Effect on spirituality (using the Spirituality Scale): *Changes in Biochemical indices during KPT-sessions: *EEG Power spectrum modulations during KPT-sessions.

Additional relevant information	*Content analysis data (the participant`s descriptions of experiences during KPT) used to establish efficacy of treatment.
Author conclusions, interpretations, and recommendations	*Results suggest that KPT increases the efficacy of conventional alcoholism treatment and contribute significantly to their sobriety. *The more negative experiences during KPT, the longer remissions were observed – underscores the importance of addressing negative aspects of alcoholism during KPT. *The authors believe the efficacy of KPT can be interpreted from psychodynamic, hypnotherapeutic/ suggestive, and spiritual perspectives.
Group	**Krupitsky et al. 1992**
Source	Alcoholism Treatment Quarterly
Trial identification	Not identified
Study period	Not reported
Study location	Russia
Type of addiction	Alcoholism
Population, n (male/female) Age	n=186 (186/0) Mean age 33.4±1.07 (active) and 38.4±0.47 (control)
Diagnosis (Criteria for diagnosis)	Treatment-resistant, unable to maintain sobriety for a 3-month period, experienced withdrawal symptoms
Concomitant drug use	Not reported
Psychiatric comorbidities	Not reported
Study design	Randomized clinical trial
Purpose	To assess the efficacy of the Affective Contra-Attribution (ACA) method in degree of abstinence, compared to traditional treatment of alcohol dependence
Psychedelic substance	Ketamine Dose: 3.0 mg/kg Administration: Intramuscular Times administered: 1
Control substance	Conventional pharmacological and therapeutic treatment of AUD; aversive emetic therapy, pharmacological treatment of craving, and individual and group therapy
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	No
Study measures	*Patient self-reporting
Behavioral outcome	Abstinence for at least 1 year (69.8% vs. 24%) and low relapse rates (27.9% vs. 76%).
Timeline for treatment/ intervention	1-day ketamine treatment with the ACA method, combining aversion therapy and psychedelic therapy for patients with alcohol dependence. *Patients are recruited from a clinic using traditional methods for AUD (aversive emetic therapy, pharmacological treatment of craving, individual and group therapy aimed at promoting abstinence). *Patients were treated for 3 months without results. *2-3-hour session with preparations, explaining and orientation. *1.5-2-hour session with ketamine and psychotherapy with a psychotherapist and a anesthesiologist. *2-4-hour session with group therapy aimed at inpatient awareness of the negative experience of alcohol.
Primary outcome(s)	*End of study (1-year) abstinence: 69.8% (n=60/86) vs. 24% (n=24/100).
Secondary outcome(s)	*Relapse rates: 27.9% (n=24/86) vs. 76% (n=76/100). *Lost to follow-up: 2.3% (n=2/86).

Additional relevant information	
Author conclusions, interpretations, and recommendations	*Lasting memories of the destructive effects of alcohol (with recall of negative emotional states) effectively changed the patient's lifestyle. *The interaction between the patient and the therapist during the treatment seemed to imprint an unconscious and deep awareness of the destructiveness of alcohol and that lifestyle. *The interpretative feature was a decisive element in the effectiveness of this approach.
Group	**Sessa et al. 2021**
Source	Journal of Psychopharmacology
Trial identification	NCT04158778
Study period	April 2018 – June 2020
Study location	UK University of Bristol, Bristol
Type of addiction	Alcoholism
Population, n (male/female) Age	n=14 (8/6) Age 18-65
Diagnosis (Criteria for diagnosis)	AUD (DSM-IV for AUD)
Concomitant drug use	Yes
Psychiatric comorbidities	Yes
Study design	Open label, proof of concept feasibility study
Purpose	Assess if MDMA-assisted psychotherapy can be delivered safely and be tolerated by patients with AUD, as well as improve study outcomes related to abstinence and quality of life
Psychedelic substance	MDMA Dose: 25 mg + 62.5 mg Administration: Oral Times administered: 2
Control substance	No control
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	No
Study measures	*Questionnaires/ rating scales (PHQ-9, GAD-7, SADQ, SIP, CIWA, SUDS, C-SSRS) *Timeline Follow Back *Physical health check *Psychiatric assessment
Behavioral outcome	Completion of trial and changes in drinking habits.
Timeline for treatment/ intervention	<u>10-week psychedelic-assisted psychotherapy for treating alcoholism with MDMA.</u> 1) Community alcohol detoxification prior to treatment. 2) 10 psychotherapy sessions over 8 weeks. 3) MDMA distribution at session 3 and 7 (6–8-hour sessions). 4) Temperature, blood pressure and heart rate were monitored during sessions. 5) Observations the night after MDMA-sessions and sessions the morning after, and telephone-sessions for 6 days after. 7) Remaining sessions using motivational interviewing and cognitive behavioral approaches (1-hour sessions) 7) No control groups 8) Participants received questionnaires about their use or desire to use illicit ecstasy outside of the study to monitor the risks of illicit use.

	9) Additional follow-up questionnaires at the end of the trial 10) Long-term follow-up data was collected at three, six and nine months
Primary outcome(s)	*Completing trial: 12 *Receiving booster-dose: 11 *Adverse events: No adverse events were reported.
Secondary outcome(s)	*Changes in drinking behavior (units per week consumed at three, six and nine months since completion of detoxification): From 130.6 units alcohol per week to less than 14 units per week for 11 of the 12 participants (as well as total abstinence for 9 of these). n=3 relapsed to drinking more than 14 units per week after the 9-month follow-up. On average, the alcohol consumption had risen back to 18 units per week at the 9-month follow-up. *Measure of mental well-being, psychosocial function, and quality of life: POMS for 7 days after each MDMA session showed no evidence of mood disturbance among the participants. Brief assessments of mood and anxiety made at baseline, after the 8-week course, and at the three-, six- and nine-month follow-up, using the PHQ-9 and GAD-7 rating scales – showed a reduction in anxiety and depression at baseline, a transient increase at three months, followed by a further reduction at six months and a moderate increase at nine months. C-SSRS screening showed no increase in suicidality. *Measures of concomitant drug use: Most patients were also using medication for anxiety and/or depression.
Additional relevant information	
Author conclusions, interpretations, and recommendations	*MDMA`s capacity to increase feelings of empathy and compassion for the self and others can contribute to improved self-awareness and subsequently reduce the denial of harmful use of alcohol. *The next logical step is to conduct a placebo-controlled randomized controlled trial with consistent levels of therapist contact between conditions, enabling any group differences in clinical outcomes attributes to the MDMA rather than the psychological support provided.
Group	**Dakwar et al. 2014**
Source	Biological Psychiatry
Trial identification	NCT01790490
Study period	February 2011 – March 2012
Study location	USA New York State Psychiatric Institute
Type of addiction	Cocaine addiction
Population, n (male/female) Age	n=8 (7/1) Mean age 47.5±5.5
Diagnosis (Criteria for diagnosis)	OUD (DSM-IV for OUD)
Concomitant drug use	No
Psychiatric comorbidities	No
Study design	Triple-blind, randomized controlled crossover trial
Purpose	Assess the effects of ketamine on SUD, the tolerability of two doses and how they affect cue-induced craving and motivation to quit
Psychedelic substance	Ketamine (K1) Dose: 0.41 mg/kg Administration: Intravenous Infusion length: 52 minutes Times administered: 1 Ketamine (K2) Dose: 0.71 mg/kg Administration: Intravenous

	Infusion length: 52 minutes Times administered: 1
Control substance	Lorazepam (LZD) Dose: 2.0 mg Administration: Intravenous Infusion length: 52 minutes Times administered: 1
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	Yes
Study measures	*Questionnaires/ rating scales (URICA, VAS, CADSS, BPRS) *Timeline Follow Back *Urine toxicology *Health check *Psychiatric assessment
Behavioral outcome	Reduced cocaine use (amount and frequency) or complete abstinence.
Timeline for treatment/ intervention	9-day ketamine treatment with 3 counter-balanced infusions for cocaine dependence. *Day 1: Baseline measures collected. *Day 1-3: Attained abstinence. *Psychological preparation and pr.inf. relaxation exercises. *Day 4: First infusion. *Participants were monitored for 2h po.inf. *10-minutes mindfulness-based exercises po.inf. *Interviews 20-minutes and 1h po.inf. for assessments (BPRS, CADSS). *All 3 substances administered to all participants, separated by 48h. *Day 9: Discharge. *Participants were assessed weekly for 4 weeks.
Primary outcome(s)	*Tolerability of 2 doses of Ketamine: Well tolerated. Mild to moderate sedation, low and comparable drug-liking scores, some BT elevation. *Change in cue reactivity (from baseline to 24h po.inf., using sum VAS scores): Significantly decreased craving (median 65 vs. -126) K1 relative to LZP and (median 53 vs. -18) K2 relative to LZP. *Change in motivation to quit (using URICA, 0-13. Baseline and 24h post infusions): Significantly increased motivation to quit (median 0.15 vs. 3.6) K1 relative to LZP, and NO significantly increased motivation to quit K2 relative to LZP.
Secondary outcome(s)	*Reduction in cocaine use (using TLFB and utox): Baseline $149.30/use/day vs. Follow-up $10.50/use/day. Baseline 22/28 days of use vs. Follow-up 5/28 days of use. n=4 demonstrated 2+ weeks of abstinence (also presented with post-K1 URICA scores exceeding 11.5).
Additional relevant information	*Those who demonstrated 2+ weeks of abstinence (n=4) also had post-K1 URICA scores exceeding 11.5 – this motivational score corresponds to maintenance. *No psychotherapy or behavioral treatment (participants will be given referrals if necessary)
Author conclusions, interpretations, and recommendations	*Tolerability shows great promise for ketamine infusions when administered under safe and controlled conditions. *The glutamatergic actions of ketamine may address dependence-related adaptions, as well as anti-depressant efficacy. *Motivation to quit may be responsive to pharmacotherapy (previously only believed to respond to PT). *Future research needed to expand on these findings.
Group	Dakwar et al. 2017
Source	Molecular Psychiatry
Trial identification	NCT02596022
Study period	June 2013 – July 2015
Study location	USA New York State Psychiatric Institute

Type of addiction	Cocaine addiction
Population, n (male/female) Age	n=20 (11/9) Mean age 48.6±6.1
Diagnosis (Criteria for diagnosis)	SUD (Active dependence with at least 8 days of use or 4 binges of large amounts over the past 30 days, and at least one positive utox during screening)
Concomitant drug use	No
Psychiatric comorbidities	No
Study design	Double-blind, randomized controlled, crossover trial
Purpose	To detect behavioral shifts in the relative salience of cocaine now vs. money later, longer than 24 hours post-infusion
Psychedelic substance	Saline Administration: Intravenous Infusion length: 50 minutes Bolus: Saline, 2 minutes Times administered: 1 Ketamine Dose: 0.60 mg/kg Administration: Intravenous Infusion length: 50 minutes Bolus: 0.11 mg/kg ketamine/saline, 2 minutes Times administered: 2
Control substance	Midazolam Dose: 0.025 mg/kg Administration: Intravenous Infusion length: 50 minutes Bolus: Saline, 2 minutes Times administered: 2
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	Yes
Study measures	*Questionnaires/ rating scales (HDRS, DES-11, CADSS, FFMQ, VAS-C) *Urine toxicology *Health check *Psychiatric assessment
Behavioral outcome	Reduced self-administration of cocaine and use in natural ecology.
Timeline for treatment/ intervention	3x 6-day ketamine treatment for cocaine dependence. *Participants were hospitalized 3x for 6 days at a time, each separated by 2 weeks. *Infusion the 1st hospitalization was Saline (to exclude those who does not choose cocaine in the “choice session”). *Day 1-2: Washout. *Day 3: 28-minute “sample session” with administration of 2 obligatory free-base cocaine doses (25 mg). *Day 4: 52-minute infusion. *Monitoring with HR, BP and SPO_2 throughout treatment and (up to) 2 hours after. *Safety and psychiatric evaluation with psychiatrist after monitoring. *Relaxation and breathing exercises. *Various assessments completed after treatment. *Day 5: 70-minute “choice session” of 5 choices (25 mg cocaine vs. $11). *Day 6: Discharge. *Met 3x/weekly with research staff for 2 weeks following each hospitalization for follow-up (utox).

Primary outcome(s)	*Reduction in self-administration of cocaine (saline/baseline vs. Ketamine vs. Midazolam): 67% vs. 10% reduction in self-administration from saline/baseline to 28h post ketamine. On average 1.61 cocaine choices (ketamine) vs. 4.33 cocaine choices (Midazolam).
Secondary outcome(s)	*Ketamine's effect on non-reactivity (using the non-reactivity subscale (1-5) of the FFMQ): Ketamine 3.46 vs. Midazolam 2.92 (lasting at least 48h after infusion). Saline infusion ca. 2.80. *Reduced cocaine use in natural ecology (calculated in $ for each time-point during the 2-week follow-ups): Initial reduction $22.45 vs. $3.20 – ceased to separate from Midazolam after several days. *Reduced cocaine craving (using a 100-mm VAS-C): Significant reduction for ketamine-group vs. Midazolam-group (ca. 60% vs. ca. 15%) – not sustained throughout monitoring period.
Additional relevant information	*The 1st "sham" infusion with saline served as baseline for self-administration of cocaine. *No psychotherapy or behavioral treatment.
Author conclusions, interpretations, and recommendations	*Sustained efficacy still not determined – relapse prevention treatments to leverage the effects into persistent behavioral change? *Behavioral treatment might be necessary to target dependence related deficits and facilitate behavioral modification. *Extension to clinical setting to refine/better dependence-related vulnerabilities.
Group	Dakwar et al. 2019
Source	American Journal of Psychiatry
Trial identification	NCT01535937
Study period	September 2011 – December 2016 (February 2012 – April 2017)
Study location	USA New York State Psychiatric Institute
Type of addiction	Cocaine addiction
Population, n (male/female) Age	n=55 (41/14) Age not reported
Diagnosis (Criteria for diagnosis)	SUD (DSM-IV for SUD)
Concomitant drug use	No
Psychiatric comorbidities	No
Study design	Double-blind, randomized controlled trial
Purpose	Test whether a single ketamine infusion improves abstinence and time to relapse in patients with SUD engaging in MBRP-treatment.
Psychedelic substance	Ketamine (n=27) Dose: 0.5 mg/kg Administration: Intravenous Times administered: 1
Control substance	Midazolam (n=28) Dose: 0.025 mg/kg Administration: Intravenous Times administered: 1
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	Yes
Study measures	*Questionnaires (HDR, DES-II, VAS, FFMQ, PSS, CADSS) *Timeline Follow Back

	*Health check *Psychiatric assessment *Utox
Behavioral outcome	Abstinence following treatment in Ketamine vs. control Midazolam. Ketamine`s effect on craving and time to relapse.
Timeline for treatment/ intervention	5-week ketamine-assisted trial with MBRP for treating cocaine dependence. *5 days hospitalization with MBRP (mindfulness-based relapse prevention) and daily sessions of behavioral treatment. *A 40-minute ketamine/midazolam infusion on day 2, with a MBRP session 2 hours after infusion. *Participants were provided with breathing exercises and other practices to prepare for the infusions. *Participants were discharged on day 5. *Participants returned twice weekly for 4 weeks for MBRP sessions. *Participants received referrals to other treatments at the end of the trial. *Additional follow-up interviews over telephone after 6 months.
Primary outcome(s)	*2-weeks of end-of-study abstinence (confirmed with toxicology): 48.2% (13/27) for ketamine-group, 10.7% (3/28) for midazolam-group. 57.7% (ket) vs. 92.9% went on to use cocaine or dropped out. The ketamine-group were 53% less likely to relapse. *Abstinence at 6-month follow-up: 44% in Ketamine group vs. 0% in the Midazolam group.
Secondary outcome(s)	*Weekly cocaine use (during week 2 through 5): Odds of cocaine use 7.8 times greater in midazolam-group (with no change of use over time in both groups). *Weekly craving scores (during weeks 1-5): 58.1% lower scores in ketamine-group (with no change in cravings over time in both groups).
Additional relevant information	
Author conclusions, interpretations, and recommendations	*Documentation of ketamine being well tolerated and promoted abstinence, especially compared to the control group, when administered in combination with MBRP. *Need for a larger sample to clarify mechanisms, examine the synergy between ketamine and behavioral treatments, and evaluate alternatives to this.
Group	**Jovaisa et al. 2006**
Source	Medicina (Kaunas)
Trial identification	NCT00300794
Study period	February 2003 – June 2006
Study location	Lithuania Vilnius University Emergency Hospital
Type of addiction	Opioid addiction
Population, n (male/female) Age	n=50 (43/7) Age 18-35
Diagnosis (Criteria for diagnosis)	OUD (DSM-IV or ICD-10 for OUD)
Concomitant drug use	No
Psychiatric comorbidities	No
Study design	Double-blind, randomized controlled trial
Purpose	Evaluate the effect of subanesthetic ketamine infusion for suppressing opiate withdrawal symptoms; the long-term effects; subsequently, abstinence and post-infusion treatment retention
Psychedelic substance	Ketamine Dose: 0.5 mg/kg/h Administration: Intravenous

	Bolus: 0.5 mg/kg Times administered: 1
Control substance	Saline Administration: Intravenous Times administered: 1
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	No
Study measures	*Questionnaires/rating scales (SOWS, OOWS, health and socio-legal issues, ASI) *Health check *Psychiatric assessment *RAI-protocol (for assessing cardiovascular response, respiratory response, and plasma cortisol levels)
Behavioral outcome	Reduced opioid use and/or complete abstinence. Initiation and completion of aftercare program.
Timeline for treatment/ intervention	5-day inpatient RAI under ketamine anesthesia for suppression of withdrawal symptoms in opioid addicts. *A 2-day hospitalization for morphine stabilization, dosed at 5-10 mg morphine hydrochloride, intramuscular (based on SOWS and OOWS). *Ketamine anesthesia administered 9pm on day 3 – started 5 minutes before RAI. *A strict RAI-protocol was used during treatment. *Measurements made every 10 minutes and summed together each hour (for 3hrs post-infusion), as well as the first the first 24 (plasma cortisol levels) and 48 (SOWS and OOWS) hours. *Obligatory: requirement to have an aftercare plan after discharge (abstinence-based, naltrexone-supported outpatient counseling, residential rehabilitation program). *Follow-up at 4 months with questionnaire (based on Addiction Severity Index) and utox.
Primary outcome(s)	*Cardiovascular response: More stable hemodynamic profile for ketamine. *Respiratory response: Lower peak rise for ketamine. *Renal and gastrointestinal response: No significant changes or differences between groups. *Severity of opiate withdrawal (during anesthesia phase, using OOWS-A): Significantly higher in control. *Minimum alveolar concentration (MAC) of isoflurane (during anesthesia phase): Significantly higher in control. *Trends in plasma cortisol levels (during the first 24hrs): Significant suppression for ketamine, not for control. Morning after rise is cortisol levels significantly higher in control than ketamine.
Secondary outcome(s)	*Follow-up rate: 90% (n=45/50). *Reported social/family life improvement: ca. 48% (ketamine) vs. 27% (placebo). *Reported health improvement: ca. 86% (ketamine) vs. 67% (placebo). *Retention in aftercare program: 37% (ketamine) vs. 25% (placebo). Outpatient counseling programs; ketamine (n=13/21) vs. placebo (=19/24). Residential rehabilitation programs; ketamine (n=8/21) vs. placebo (n=5/24). *Complete abstinence (at 4-month follow-up): ca. 18% (ketamine) vs. ca. 15% (placebo). *Abstinence length (in weeks, on average): 9.4±6.6 (ketamine) vs. 8.0±7.0 (placebo).
Additional relevant information	
Author conclusions, interpretations, and recommendations	*More significant differences between ketamine and control groups during the acute phase of RAI, and minor to no differences at the end of procedure. *As a single agent administered at infusion rates of 0.3 and 0.5 mg/kg/h, ketamine does not induce general anesthesia and complex hallucinations – can this be why there are so low results for follow-up abstinence?
Group	**Krupitsky et al. 2002**
Source	Journal of Substance Abuse Treatment

Trial identification	Not identified
Study period	Not reported
Study location	Russia St. Petersburg Research Center of Addictions and Psychopharmacology
Type of addiction	Heroin addiction
Population, n (male/female) Age	n= 70 (55/15) Age 18-30
Diagnosis (Criteria for diagnosis)	OUD (DSM-IV or ICD-10 for OUD, present at least 1 year)
Concomitant drug use	No
Psychiatric comorbidities	No
Study design	Double-blind, controlled randomized trial
Purpose	To assess the safety and efficacy of KPT for patients with OUD, using one high-dose and one low-dose group to compare psychedelic experience, abstinence, craving, and positive change in nonverbal unconscious emotional attitudes
Psychedelic substance	Ketamine Dose: 2.0 mg/kg Administration: Intramuscular Treatment length: 1.5-2 hours Times administered: 1
Control substance	Ketamine Dose: 0.2 mg/kg Administration: Intramuscular Treatment length: 1.5-2 hours Times administered: 1
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	Yes
Study measures	*Questionnaires/ rating scales (ZDS, VAS-C, SA, HRS, MMPI, LCS, CTA, PLT, SCS, SIDI) *Urine toxicology *Interviews with family/friends *Health check *Psychiatric assessment
Behavioral outcome	Greater rate of abstinence within follow-up (long-term, long-lasting change).
Timeline for treatment/ intervention	3-5-day single session ketamine psychotherapy for heroin dependence. *KPT 1/3: 10 hours preliminary psychotherapy for preparation prior to ketamine infusion – the treatment`s foundation for success. *KPT 2/3: 1.5-2-hour ketamine psychotherapy sessions with 2 physicians, 1 psychotherapist, and 1 anesthesiologist. *n=35 received high-dose ketamine and n=35 received low-dose ketamine, which acts as an active placebo. *Sett and setting, content and direction customized for each patient. *A detailed self-report is written the same evening. *KPT 3/3: 5 hours reflective and evaluating psychotherapy to help integrate new insights into everyday life. *Assessments done pre-therapy (baseline), post-therapy (during the week after ketamine inf.), 1, 3, 6, 12, 18, and 24 months.
Primary outcome(s)	*Rate of abstinence (from baseline to 24 months): Abstinence significantly higher in high-group (emerged at 1st month of follow-up and through the 23-weeks). Abstinence in high-group also higher than abstinence in conventional treatment programs for heroin addicts in Russia.

	*Rate of relapse (from baseline to 24 months): Corresponding relapse rate in high-group lower than low-group. Almost 50% in high-group and 60% in low-group relapsed within the 3 first months.
Secondary outcome(s)	*Craving for heroin (VASC): Both groups significantly reduced heroin craving. High-dose 29.24 (pre-treatment) vs. 3.97 (post-treatment), low-dose 36.34 vs. 15.06. Continued reduced craving during follow up for high-dose, but one 1st month for low-dose. *Syndrome of anhedonia (SA): Significant reduced severity of all 3 components. Scores show positive effect for high-dose, but not statistically significant. *Anxiety (SAS): Significant reduced anxiety in both groups, with no significant difference. *Depression (ZDS): Significant reduction relative to baseline, maintained though follow-up. No difference between groups. *MMPI (improvement in following personality characteristics): High-dose 6/17 (depression, conversation hysteria, paranoia, schizophrenia, Taylor scale of Anxiety, self-sufficiency), low-dose 10/17 (hypochondriasis, depression, conversation hysteria, masculinity-femininity, paranoia, psychasthenia, schizophrenia, sensitivity-repression, Taylor scale of Anxiety, self-sufficiency). No significant difference between groups. *Locus of control (using the LCS(scale), perceived control and management of own life): Significantly more "internal" after KPT in both groups. High-dose index 4.1±1.5 (pre-treatment) vs. 5.2±2.1 (post-treatment). Low-dose index 3.8±1.3 vs. 4.5±1.4. Locus of Control of failures significantly more internal in high-dose post-treatment vs. baseline (5.2±1.8 vs. 4.2±2.0). *Understanding the meaning and purpose of one`s life: Significant increase in "meaning of life", "understanding purpose of life", and "self-actualization", no statistically significant difference between groups. *Spirituality (SCS, spirituality change score): High-dose 27.2±9.3 vs. low-dose 25±9.6. *Non-verbal emotional attitudes (using CTA): Significant positive change in 7/9 in high-dose vs. 4/9 in low-dose. *Adverse events: No complications reported.
Additional relevant information	*Acute psychological responses (Hallucinogen Rating Score, HRS): High-dose had full psychedelic experience. Low-dose had some drug effects without full psychedelic experience. Score-differences between groups statistically significant 5/6 (not volition).
Author conclusions, interpretations, and recommendations	*This treatment is more effective with high dose of ketamine. *High-dose ketamine elicits full psychedelic experience. *Low-dose ketamine elicits "sub-psychedelic" experience. *More research to explore how to utilize ketamine psychotherapy`s unique psychological effects to promote abstinence. *First; repeated or single session more effective?
Group	**Krupitsky et al. 2007**
Source	Journal of Psychoactive Drugs
Trial identification	Not identified
Study period	Not reported
Study location	Russia St. Petersburg Pavlov State Medical University
Type of addiction	Heroin addiction
Population, n (male/female) Age	n=59 (49/10) Age 18-35
Diagnosis (Criteria for diagnosis)	OUD (DSM-IV or ICD-10 for OUD, present at least 1 year)
Concomitant drug use	No
Psychiatric comorbidities	No
Study design	Double-blind randomized trial

Purpose	Assessing the efficacy of single vs. repeated session ketamine-assisted PT for abstinence, reduction in craving and positive change in nonverbal unconscious emotional attitudes
Psychedelic substance	Ketamine Dose: 2.0 mg/kg Administration: Intramuscular Treatment length: 1.5-2 hours Times administered: 3
Control substance	Ketamine Dose: 2.0 mg/kg Administration: Intramuscular Treatment length: 1.5-2 hours Times administered: 1
Pre-registration (Analysis plan and/or srudy protocol)	No
Adverse events	Yes
Study measures	*Questionnaires/ rating scales (ZDS, SAS, VASC, PLT) *Timeline Follow Back *Interviews (with patient and relatives) *Health check *Psychiatric assessment *Utox
Behavioral outcome	Abstinence for at least 1 year (50% vs. 22.2%) and low relapse rate (10.17%, not statistically significant between groups)
Timeline for treatment/ intervention	3-month comparison of repeated vs. single session KPT for heroin addicts. *Inpatient detoxification prior to treatment. *All (n=59) received 1st KPT-session with 5hr PT (psychotherapy) + ketamine-infusion + 5hr PT. *Discharge, randomization. *1-month: Repeated KAP-group (n=26) received 1hr AC (addiction counseling) + ketamine-infusion + 1hr PT. Single KAP-group (n=27) received 1hr AC. *2-months: Repeated KAP-group received 1hr AC + ketamine-infusion + 1hr PT. Single KAP-group received 1hr AC. *1-year follow-up at 1, 3, 6, 9 and 12 months after 3rd/final treatment (interviews, utox, physical exam, (blinded) TLFB, ZDS, SAS, VASC, PLT).
Primary outcome(s)	*Rate of abstinence: Difference in follow-up abstinence rate statistically significant between groups. 50% (n=13/26) vs. 22.2% (n=6/27) abstinence at 1 year follow-up. *Treatment retention: 10,17% (n=6/59) relapsed within 1-month of 1st KPT-session. Difference in treatment retention not statistically significant between groups. 15.4% (n=4/26) relapsed prior to 3rd KPT-session vs. 25.9% (n=7/27) relapsed after 1st AC.
Secondary outcome(s)	*Psychometrics (depression ZDS, state-trait anxiety SAS, craving for heroin VASC): Significant reduction after 1st KPT-session with gradual decrease. No significant difference between groups. *Understanding the meaning of life (using PLT): Significant increase after 1st KPT-session with gradual increase. No significant difference between groups.
Additional relevant information	*Side effects: Acute increase in systolic and (particularly) diastolic BP of 20-30% during KPT-sessions in all patients.
Author conclusions, interpretations, and recommendations	*High abstinence rates in the repeated KPT-group indicates that multiple sessions are better than single session, despite lack of significant differences between groups in psychometrics. *Lack of significant differences between groups suggest that the increased abstinence rate in the repeated session-group is at least partly due to factors not measured in this study. *This effect could be related to “afterglow”. *Future research with employed measures to capture this effect.
Group	**Lalanne et al. 2016**
Source	BMC Psychiatry

Trial identification	Not identified
Study period	2015
Study location	France Rheumatology department, Strasbourg University Hospital
Type of addiction	Opioid addiction
Population, n (male/female) Age	n=1 (0/1) Age 36
Diagnosis (Criteria for diagnosis)	Opioid-induced hyperalgesia (DSM-IV for OUD)
Concomitant drug use	Yes
Psychiatric comorbidities	Yes
Study design	Case report
Purpose	To test opioid tapering using oral ketamine to reduce withdrawal symptoms and successfully reduce the need for opioids
Psychedelic substance	Ketamine Dose: 1.0 mg/kg (5.0 mg/ml) Administration: Oral Times administered: 1
Control substance	No control
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	Yes
Study measures	*Questionnaires/rating scales (COWS) *Clinical and psychiatric observations *Measure of craving and pain not reported
Behavioral outcome	Clear reduction of prescription opioids.
Timeline for treatment/ intervention	Case report of ketamine-assisted opioid tapering in addicted woman from subsequent pain management. *Transfer to psychiatric department. *Single infusion 1.0 mg/kg oral administration. *Gradual reduction in opioid treatment, 10% every other day. *Monitoring to avoid withdrawal symptoms, with medication ready if necessary. *Discharged after 3 weeks, as stay was delayed due to the patient needing a break from treatment. *Nurse controlled administration of prescription opioids after treatment. *Functional re-education organized.
Primary outcome(s)	*Reduction in prescription opioids: Baseline (Diazepam 10 mg 3/daily + Hydroxyzine 100 mg 2/daily + Venlafaxine 150 mg/day + Oxycontin 60 mg 2/daily + Oxycodone 10 mg every 4th hour + Acetaminophen/ Codeine 300 mg/25 mg 6/daily) vs. post-treatment (Codeine 50 mg 3/daily).
Secondary outcome(s)	*Withdrawal symptoms: None to report. *Pain: None to report. *Cravings: None to report.
Additional relevant information	*Administration of ketamine before opioid tapering reduced lumbosacral pain and counteracted withdrawal signs due to the opioid tapering. *The patient presented with emotional and paranoid reactions, which resulted in a break from the treatment plan. *The remaining opioid medication post-treatment is administered by a nurse. *Functional re-education organized. *No mention of therapy or behavioral treatment.

Author conclusions, interpretations, and recommendations	*Propose ketamine for opioid withdrawal instead of (many) other psychotropic treatments – feasible. *Propose testing of ketamine for opioid withdrawal in a proof of concept, open label study.
Group	**Ocker et al. 2020**
Source	Pain Practice
Trial identification	Not identified
Study period	Not reported
Study location	USA Thomas Jefferson University Hospital, Philadelphia, Pennsylvania
Type of addiction	Opioid addiction
Population, n (male/female) Age	n=1 (male) Age 55
Diagnosis (Criteria for diagnosis)	Opioid-induced hyperalgesia and CRPS-I (Diagnostic criteria not reported)
Concomitant drug use	No
Psychiatric comorbidities	Not reported
Study design	Case report
Purpose	Test whether a multimodal, integrated ketamine-approach can promote successful opioid tapering, reduce pain, withdrawal symptoms and promote long-term abstinence
Psychedelic substance	Ketamine Dose: 0.09-0.6 mg/kg Administration: Intravenous Times administered: 5-day continuous infusions Ketamine Dose: Up to 0.77 mg/kg Administration: Intravenous Times administered: 5-days continuous infusions
Control substance	No control
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	Yes
Study measures	*Numeric rating scale (for pain assessment) *Assessment tools for alcohol withdrawal symptoms, adverse effects, and tolerability of treatment not reported.
Behavioral outcome	Complete abstinence from prescription opioids as a result of pain management.
Timeline for treatment/ intervention	5-day continuous ketamine infusions and CBT for opioid dependence following treatment of chronic pain. *Day 1 dosing start at 0.09 mg/kg/h, with possibility for larger dose as tolerance is built. *Withdrawal symptoms, hallucinations or other acute effects will be medicated if necessary. *Pain assessment will be done every treatment day, discharge-day, after 30 days, 6 months and 1 year. *Prescription of opioids were given. *Outpatient CBT every 3 to 4 weeks via telemedicine. *Meetings with psychiatrist every 3 months through follow-up year. *Pain at 2/10 by month 6, additional 5-day continuous ketamine infusions (max 0.77 mg/kg/h).

	*Pain at 4/10 by 1 year, additional 5-day continuous ketamine infusions planned.
Primary outcome(s)	*Reduction in pain: From 9/10 (day 1) to 0/10 (day 5/discharge), 2/10 to 0/10 (6 months), and 4/10 (1 year). *Complete abstinence from high-dose opioids (throughout the treatment and 1-year follow-up): Complete abstinence throughout treatment and 1-year follow-up period. Did not use the prescribed opioids after discharge. *Minimal amount of withdrawal symptoms: Total 168 MME Oxycodone administered for withdrawal symptoms.
Secondary outcome(s)	
Additional relevant information	*Infusion reduced by 50% and discontinued in the afternoon on day 5 (discharge). *The patient experienced dramatically improved function (physical) and improved family time.
Author conclusions, interpretations, and recommendations	*Case study showing how an integrated approach took advantage of ketamine`s unique pharmacological effects in combination with CBT can successfully enable a rapid opioid taper. *This is one possible strategy for accomplishing these tasks in a motivated patient.
Group	**Pradhan and Rossi 2020**
Source	Cureus
Trial identification	Not identified
Study period	Not reported
Study location	USA Cooper University Hospital, Camden
Type of addiction	Opioid addiction
Population, n (male/female) Age	n=3 Gender and age not reported
Diagnosis (Criteria for diagnosis)	OUD (Diagnostic criteria not reported)
Concomitant drug use	Not reported
Psychiatric comorbidities	Not reported
Study design	Open label, proof of concept study
Purpose	To test the feasibility and efficacy of ketamine, rTMS, and TIMBER in patients with OUD
Psychedelic substance	Ketamine Dose: 0.75 mg/kg Administration: Intravenous Infusion length: 45 minutes (stopped at 745 mg total) Bolus: Times administered: 1
Control substance	No control
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	No
Study measures	*The Opiate Craving Scale (OCS: scores range 0-30) *Assessment Scale for Mindfulness Interventions (ASMI) *EEG with HR variability during treatment
Behavioral outcome	No behavioral outcome.
Timeline for treatment/ intervention	3-week trial investigating the feasibility and efficacy of ketamine, rTMS, and TIMBER for OUD. *Single infusion 0.75 mg/kg ketamine over 45 minutes (745 mg max).

	*A 1-week washout period. *5 rTMS-sessions with 10 Hz and 3000 applied stimulation pules, over a 1–2-week period. *5 TIMBER mindfulness-based therapy sessions during the same 1-2 weeks. *2 times daily home practice and additional sessions on an as-needed basis for cravings.
Primary outcome(s)	*Reduction in craving (using the OCS, from baseline (day 1) to the 5th rTMS-session (week 3)): Baseline 23.66 vs. 5th session 8.33, 65.7% decrease.
Secondary outcome(s)	*Increase in Mindfulness (using the ASMI, from baseline (day 1) to the 5th rTMS-session (week 3)): Baseline 29 vs. 5th session 49.33, 41.21% increase.
Additional relevant information	*2/3 with heroin dependence. *1/3 with Oxycodone dependence. *Trauma Interventions using Mindfulness Based Extinction and Reconsolidation of memories (TIMBER) *Mindfulness-based graded exposure therapy (MB-GET)
Author conclusions, interpretations, and recommendations	*Limited research but promising – at least as individual treatments. *The combination therapy is feasible for patients with OUD. *Reduces craving, promotes abstinence, and reduces the amount used in OUD-patients.
Group	**Azhari et al. 2021**
Source	The American Journal of Drug and Alcohol Abuse
Trial identification	NCT02946489
Study period	October 2016 – August 2018
Study location	USA New York State Psychiatric Institute
Type of addiction	Cannabis addiction
Population, n (male/female) Age	n=8 (4/4) Mean age 42.5±13.5
Diagnosis (Criteria for diagnosis)	CUD (DSM-IV for CUD with at least 5 days of use per week for the last 30 days, confirmed with urine toxicology)
Concomitant drug use	No
Psychiatric comorbidities	No
Study design	Single-blind, proof of concept trial
Purpose	Assess the impact of ketamine in combination with MET and MBRP on motivation to quit, reduce cravings and promote abstinence
Psychedelic substance	Ketamine (ADM1) Dose: 0.6 mg/kg Administration: Intravenous Infusion length: 50 minutes Bolus: 0.11 mg/kg ketamine/saline, 2 minutes Times administered: 1 Ketamine (ADM2) Dose: 0.6 mg/kg Administration: Intravenous Infusion length: 90 minutes Bolus: 0.11 mg/kg ketamine/saline, 2 minutes Times administered: 1
Control substance	No control
Pre-registration (Analysis plan and/or study protocol)	Study protocol published, not analysis plan

Adverse events	No
Study measures	*Questionnaires/ rating scales (VAS-C, DCQ) *Timeline Follow Back *Utox *Field sobriety test *Health check *Psychiatric assessment
Behavioral outcome	Reduced cannabis use and/or completion 3+ weeks of end of study abstinence.
Timeline for treatment/ intervention	6-week outpatient ketamine-facilitated MET and MBRP treatment for cannabis dependence. *Recruitment → Telephone screening → Comprehensive psychiatric and medical screening. *6-week treatment with 1(2) ketamine infusion(s), 3(5) MET-sessions, and 8 MBRP-sessions. *Week 1: 1st MET-session. *Week 2: 2nd MET-session + 1st ketamine session + 3rd MET-session. *Abstinence 24+hr pre-infusion. *BP and HR monitoring and guided mindfulness exercises provided during infusion. *3hr at facility post-infusion for psychiatric and medical clearance and field sobriety test before discharge. *Week 3-6: 1st-8th MBRP-session. (*Week 4: 4th MET-session + 2nd ketamine session + 5th MET-session.) *Informed possible administrations; buspirone, d-cycloserine, ketamine, midazolam, memantine. *Timeline Follow Back, utox, DCQ, and VAS-C was assessed at each visit.
Primary outcome(s)	*Number of using days/week (using TLFB, from baseline to study end): Decreased significantly from baseline (B=5.1) to post-infusion week 2 (B=0.8), and remained significant to study end (B=0.5). *3+ weeks of end of study abstinence (using TLFB and utox): 75% (n=6/8) participants.
Secondary outcome(s)	*Confidence in one`s ability to abstain from using (in stressful situations, using DCQ 0-100): Increased significantly from baseline (44.7) to end of study (87.5). *Craving (using VAS-C): No significant difference between baseline and end of study assessment of craving.
Additional relevant information	*MET intended to help with abstinence initiation and to facilitate long-term commitment. *MBRP aimed to support relapse prevention by managing craving reactivity and cultivate abstinence-related skills, practices, and perspectives.
Author conclusions, interpretations, and recommendations	*Results indicate the feasibility of integrating ketamine with MET and MBRP for treating CUD. *Shows great results in facilitating abstinence initiation and relapse prevention. *Need to understand the interactions of ketamine with behavioral treatment, and to describe ketamine`s efficacy – randomized, controlled, multiple arms for future research.
Group	**Johnson and Black 2020**
Source	International Journal of Mental Health and Addiction
Trial identification	Not identified
Study period	December 2015 – September 2019
Study location	Australia Private Australian Mental Health Clinic
Type of addiction	Addiction to stimulants and cannabis (and psychedelics)
Population, n (male/female) Age	n=1 (m=1) Age 22
Diagnosis (Criteria for diagnosis)	SUD and CUD (DSM-IV for SUD and CUD)

Concomitant drug use	Yes
Psychiatric comorbidities	Yes
Study design	Case report
Purpose	Explore the therapeutic potential of classic psychedelics in assisting with treatment of SUD (with co-occurring depression)
Psychedelic substance	Used on 5 separate occasions upon commencement of therapy. LSD Dose: 200-500 mcg Administration: Oral Times administered: 5 *500 mcg LSD + 500 mcg LSD + 200 mcg LSD + 50 mg DMT. *200 mcg LSD + 100 mg DMT. *200 mcg LSD + 100 mg DMT. *200 mcg LSD + 50 mg DMT. *200 mcg LSD (DMT Dose: 50-100 mg Administration: Inhalation Times administered: 4)
Control substance	No control
Pre-registration (Analysis plan and/or study protocol)	No
Adverse events	Not reported
Study measures	*Utox *Mystical Experience Questionnaire (MEQ-30) *Self-report of subjective experiences
Behavioral outcome	A significant positive impact on mood, the cessation of stimulant drugs, and the application of "harm reduction" towards general use of psychoactive substances.
Timeline for treatment/ intervention	Individualized CBT program with self-administration of classic psychedelics for stimulant/cannabis addiction. *Des 2015: Enrolment in individual therapy. *Jun 2017: Enrolment in the abstinence-based Matrix program (6/20 weeks completed). *Jan 2019: Last therapy session. *Mar 2019: MEQ-30 questionnaire. *Sep 2019: Final follow-up (telephone and utox). *Report of using classic psychedelics 5 times upon commencing therapy, but especially the last 2 uses were "instrumental in his recovery". *Des 2018: Last use of classic psychedelics.
Primary outcome(s)	*Achieved abstinence from stimulants: Continued use at study start (Des 2015) until Sep 2016. Complete abstinence confirmed through utox (approximately 2.5 years). *Achieved abstinence from cannabis: Daily use reduced to nightly use Oct 2017, and weekly use from Jan 2018 till study end (Sep 2019). Wish to reduce, but not complete abstinence.
Secondary outcome(s)	*Improvement in depressive disorder: Rated as severe at initial assessment but stabilized from May 2016 to Jun 2017. Some elevation late 2017 before stabilization. Was not assessed from Dec 2018 to end of study Sep 2019. *Achieved abstinence from recreational psychedelics: High recreational doses of LSD, DMT, psilocybin and mescaline were significantly reduced, with only 2 separate used from Dec 2016 to Sep 2019 (study end). Now, only once a year.
Additional relevant information	

Author conclusions, interpretations, and recommendations	*It`s difficult to disentangle the treatment effect from the effects of the classic psychedelics consumed. *But it is clear from John`s subjective experiences with the substances that they had å significant positive impact on his mood (depression), the secession of stimulant drugs, and application of "harm reduction" in his use of psychoactive substances in general. *Useful therapeutic aids warranting further investigation, based on the psycho-spiritual and neurophysiological effects.

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