Evidence Brief: Psychedelic Medications for Mental Health and Substance Use Disorders

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the VA Office of Research and Development (ORD) and VHA Office of Mental Health and Suicide Prevention (OMHSP). The scope was further developed with input from Operational Partners (below) and the ESP Coordinating Center review team.

ACKNOWLEDGMENTS

The authors are grateful to Kathryn Vela, MLIS for literature searching, Sarah Young, MPH for study selection assistance, and the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix D in Supplemental Materials for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained.

The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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EXECUTIVE SUMMARY

Key Findings

- In a clinical research setting, use of MDMA with intensive psychotherapy led by 2 mental health professionals may improve posttraumatic stress disorder (PTSD symptom severity and result in remission for some participants in the short term (1 month to 18 weeks) (low strength of evidence [SOE]). Findings are based on several small trials of adults with moderate to severe symptoms at baseline who did not improve with prior medication or therapy trials. Most studies did not include Veterans.
- Psilocybin-assisted psychotherapy may reduce depression severity and lead to sustained remission for some participants at 12 months compared to wait list controls, but these benefits were not observed when psilocybin-assisted psychotherapy was compared to intensive psychotherapy and daily escitalopram (low SOE).
- Psilocybin-assisted psychotherapy may reduce heavy drinking days and average daily alcohol consumption among adults with alcohol use disorder (low SOE).
- Ayahuasca use may be associated with a short-term reduction in depression symptoms and suicidality (low SOE). Whether ayahuasca is effective for substance use disorder treatment is unclear.
- Ibogaine may not reduce opioid withdrawal symptoms or short-term opioid use (low SOE) and has been associated with serious adverse events including prolonged QTc, cardiac arrhythmia, and death.
- Studies conducted in the US have predominantly included non-Veteran, young, non-Hispanic white populations with access to a clinical research center or treatment program. Whether benefits can be replicated in more diverse populations and treatment settings including within VHA is unclear.
- Critical gaps to address in future research include whether treatment effects vary according to patient characteristics and disease severity and whether benefits are durable over time. The feasibility of implementing intensive psychotherapy protocols in real-world settings is another critical gap, as is determining how psychedelic treatments could fit into current standard of care and usual care pathways.

Background

The Evidence Synthesis Program Coordinating Center is responding to a request from the VA Office of Research and Development (ORD) and VHA Office of Mental Health and Suicide Prevention (OMHSP) for an Evidence Brief on the use of psychedelics for treating mental health and substance use disorders. Findings from this Evidence Brief will be used to inform VA research and clinical care.

Methods

To identify studies, we searched MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and other sources up to April 2022. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See the Methods section and our PROSPERO protocol for full details of our methodology.

CLINICAL BOTTOM LINE

MDMA-assisted psychotherapy for PTSD has been the most extensively studied therapeutic intervention involving psychedelics. Results from several small RCTs demonstrate that this

treatment may improve PTSD symptom severity to a clinically meaningful degree and lead to disease remission for some individuals in the short term. Similarly, psilocybin-assisted psychotherapy for depression shows some promise. However, study interventions included intensive psychotherapy protocols that may be challenging to implement in everyday practice. Moreover, US studies primarily enrolled young non-Hispanic white individuals and few studies included Veterans. Results may not be generalizable to more diverse populations and settings including within the Veterans Health Administration (VHA). Evidence on psychedelics for treatment of mental health and substance use disorders is therefore very preliminary. Several critical gaps need to be addressed by future research.

OVERVIEW

The term *psychedelics* refers to a group of substances that temporarily alter perception and mood and may impact numerous cognitive processes. The term is used to describe naturally derived substances with these properties, such as psilocybin, as well as synthetic substances like lysergic acid diethylamide (LSD) and 3,4-methylenedioxymethamphetamine (MDMA). Naturally derived psychedelics have been used for millennia, and starting in the 1940s through the 1960s, natural and synthetic psychedelics were used in clinical research as potential treatments for a range of medical conditions. However, study of psychedelics largely paused in the US in 1970 when most were codified as Schedule I drugs with no accepted medical use. In recent years, a growing number of researchers have been revisiting the potential therapeutic benefits of psychedelics and have sought out legal and regulatory pathways to study them.

Psychedelics and psychedelic-assisted psychotherapy have been proposed as novel treatments for adults with mental health and substance use disorders based on the supposition that intentional use of psychedelics over a limited period can disrupt problematic thought patterns, facilitate psychotherapy, and potentially lead to behavior change. New treatment options are needed given the limitations of existing therapies. The aim of this review is to inform VHA program planning by synthesizing available evidence on the benefits and harms of psychedelics as primary or adjunct treatment for mental health and substance use disorders.

From 2,532 potentially relevant articles, 15 RCTs and 23 observational studies (in 44 publications) met eligibility criteria. Studies enrolled adults with PTSD, depression, obsessive compulsive disorder (OCD), social anxiety, opioid use disorder (OUD), alcohol use disorder, tobacco use, or mixed substance use disorders and mood symptoms. Interventions involved treatment with MDMA, psilocybin, ayahuasca, 5-methoxy-N,N-dimethyltryptamine, and ibogaine with or without psychotherapy or other co-interventions.

The most extensively studied intervention involving psychedelics is MDMA-assisted psychotherapy for PTSD. We identified 9 small RCTs (including 1 study that pooled results from 6 smaller trials) and 3 observational studies of MDMA-assisted psychotherapy among adults with moderate or severe PTSD who had not improved with at least 1 past trial of medication or psychotherapy. All trials were conducted by researchers affiliated with the Multidisciplinary Association for Psychedelic Studies (MAPS) or were sponsored by this organization and thus had several features in common. Intervention group participants typically received MDMA 80–125mg with or without a 40–62.5mg supplemental dose. Comparator group participants received an 0mg placebo or a low dose of MDMA (low-dose placebo) intended to maintain participant blinding by producing some sensations of having ingested a psychedelic. Intervention and

control group participants underwent the same intensive psychotherapy protocol, typically consisting of several preparatory sessions and follow-up sessions in addition to day-long MDMA or placebo dosing sessions. Psychotherapy sessions were all co-led by 2 mental health professionals using a standardized therapy manual. If participants were receiving treatment for PTSD prior to the study start, they were required to stop it to avoid confounding and potential drug interactions with MDMA. Studies reported outcomes in terms of changes in mean total severity scores on the Clinician-Administered PTSD Scale (CAPS). Some studies reported whether participants experienced a clinically meaningful improvement in total CAPS score (defined as at least 30% improvement) and PTSD remission.

MDMA paired with intensive psychotherapy may reduce PTSD symptom severity and lead to clinically meaningful improvement and remission for some. In trials reporting these outcomes, 50% to 100% of participants experienced clinically meaningful improvements on CAPS total severity scores and remission rates ranged from 33% to 88% when assessed at 1 month to 18 weeks. Additionally, results of a meta-analysis of 7 trials indicate that participants receiving MDMA experienced significantly greater improvements in mean symptom severity compared with control group participants (pooled standardized mean difference in change scores = -0.91, 95% CI [-1.33, -0.50]). Symptoms among control group participants also improved in most studies regardless of the type of placebo used, although to a lesser degree than MDMA group participants. While the relative importance of different intervention components (MDMA, psychotherapy, and other factors such as participation effects) is unclear, a comparison of findings across trials using different forms of placebo suggests that benefits are at least partially attributable to the effects of MDMA. Although results are fairly consistent and direct, trial sample sizes are small and at risk of prognostic imbalance (a failure of randomization to balance groups on participants' responsiveness to treatment). Our confidence in these findings is low.

Other interventions involving psychedelics have been less extensively studied. Psilocybin-assisted psychotherapy for depression may reduce symptom severity and lead to sustained remission at 12 months for a proportion of recipients compared to wait list controls, but these same benefits were not observed (in a separate trial) when psilocybin-assisted psychotherapy was compared with the same psychotherapy protocol and daily escitalopram. We have low confidence in these findings, which are based on 1 small trial for each comparator. Ayahuasca use for depression may be associated with a reduction in short-term symptoms and suicidality. However, our confidence in these findings is also low due to a smaller number of trials overall with small sample sizes and some inconsistency.

Among treatments evaluated for substance use disorders, we have low confidence that psilocybin-assisted psychotherapy for alcohol use disorder may reduce alcohol consumption (heavy drinking days and the number of drinks per day) based on results of 1 small trial. Psilocybin has also been used as an adjunct to psychotherapy to reduce tobacco use, but results are limited to 1 small observational study and are insufficient to draw conclusions. Ibogaine, used most often to treat opioid withdrawal, did not improve withdrawal symptoms in 1 small trial despite observational data showing benefits. Unlike other psychedelics studied, ibogaine has been associated with serious adverse events, including death and cardiac events.

Psychedelic treatments for mental health and substance use disorders are still in an early phase of development and many gaps in the evidence exist, including whether treatment effects vary by patient characteristics or disease severity and whether observed benefits are maintained over

time. Other critical gaps in the evidence include whether psychedelic treatment protocols are reproducible and scalable in real-world settings and whether the benefits of discontinuing mental health medications to undergo psychedelic treatments outweigh the risks. In addition to addressing these gaps, areas for future research include study of Veterans with combat-related trauma and study of more diverse populations, particularly with respect to race/ethnicity, socioeconomic status, and rurality.

ES Table. Summary of Evidence

Outcome	Psychedelic	Evidence	Findings
Posttraumatic Stress Disorder			
Remission	MDMA	4 RCTs[1-4]	*Low SOE:* MDMA-assisted psychotherapy may result in PTSD remission.
Clinically meaningful improvement	MDMA	4 RCTs[2-5]	*Low SOE:* MDMA-assisted psychotherapy may result in a clinically meaningful reduction in symptom burden (defined as a ≥30% improvement on CAPS total severity scores).
Difference in symptom change scores	MDMA	7 RCTs[1-8] and 3 pre-post studies[9-11]	*Low SOE:* MDMA-assisted psychotherapy may reduce PTSD symptoms (in 7 trials, the pooled standardized mean difference in PTSD symptom change for intervention dose MDMA compared with 0mg or low-dose placebo is -0.91, 95% CI [-1.33, -0.50]).
Major Depressive Disorder			
Depressive symptoms	Psilocybin	1 RCT[12] and 3 pre-post studies[13-16a]	*Low SOE:* Psilocybin-assisted psychotherapy may reduce depressive symptoms and lead to clinically meaningful improvement (defined as ≥50% improvement on GRID-HAMD) and/or remission in some individuals.
		1 RCT[17]	*Low SOE:* Psilocybin-assisted psychotherapy may not reduce depressive symptoms compared to psychotherapy and daily escitalopram.
	Ayahuasca	1 RCT[18] and 2 pre-post studies[19,20]	*Low SOE:* Ayahuasca may reduce depressive symptoms.
Suicidal ideation	Psilocybin	1 RCT[12]	*Insufficient SOE:* It is unclear whether psilocybin reduces suicidal ideation compared to no treatment.
		1 RCT[17]	*Insufficient SOE:* It is unclear whether psilocybin reduces suicidal ideation compared to escitalopram.
	Ayahuasca	1 RCT[18,21] and 1 pre-post study[19,22]	*Insufficient SOE:* It is unclear whether ayahuasca reduces suicidal ideation compared to placebo.
Opioid Use			
Opioid use	Ibogaine	1 RCT[23] and 3 pre-post studies[24-26]	*Low SOE:* Ibogaine may not reduce short-term opioid use compared to placebo.

Outcome	Psychedelic	Evidence	Findings
Withdrawal	Ibogaine	1 RCT[23] and 5 pre-post studies[24-28]	*Low SOE:* Ibogaine may not reduce short-term opioid withdrawal symptoms compared to placebo.
Alcohol Use Disorder			
Drinking behavior	Psilocybin	1 RCT[29] and 1 pre-post study[30]	*Low SOE:* Psilocybin may decrease drinking behavior.
	MDMA	1 pre-post study[31]	*Insufficient SOE:* It is unclear whether MDMA decreases drinking behavior.
Tobacco Use			
Tobacco use	Psilocybin	1 pre-post study[32,33]	*Insufficient SOE:* It is unclear whether psilocybin influences tobacco use.
Mixed Substance Use			
Substance use	Ayahuasca	1 pre-post study[34]	*Insufficient SOE:* It is unclear whether ayahuasca reduces substance use among participants of a substance use program.
	Ibogaine	1 pre-post study[35]	*Insufficient SOE:* It is unclear whether ibogaine reduces substance use in participants of a substance use program.
Opiate or cocaine craving	Ibogaine	3 pre-post studies[36,37]	*Insufficient SOE:* It is unclear whether ibogaine reduces opiate and cocaine craving.
Other Conditions			
Social anxiety symptoms	Ayahuasca	1 RCT[38]	*Insufficient SOE:* It is unclear whether ayahuasca improves symptoms in adults with social anxiety disorder.
Obsessive compulsive symptoms	Psilocybin	1 pre-post study[39]	*Insufficient SOE:* It is unclear whether psilocybin impacts symptoms in adults with obsessive compulsive disorder.
Mood and anxiety symptoms	Ibogaine and 5-MeO-DMT	1 pre-post study[40]	*Insufficient SOE:* It is unclear whether ibogaine reduces PTSD, depressive, or anxiety symptoms in Veterans of US special operations forces.

Notes. [a] Studies included overlapping populations, 2 studies included comparison to healthy, non-treated control groups.
Abbreviations. 5-MeO-DMT=5-methoxy-N,N-dimethyltryptamine; CAPS=Clinician-Administered PTSD Scale; CI=confidence interval; GRID-HAMD=GRID-Hamilton Depression Rating Scale; MDMA=3,4-methylenedioxymethamphetamine; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial; SOE=strength of evidence.

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The ESP Coordinating Center (ESP CC) is responding to a request from the VA Office of Research and Development (ORD) and VHA Office of Mental Health and Suicide Prevention (OMHSP) for an Evidence Brief on the use of psychedelic substances for treating mental health and substance use disorders. Findings from this Evidence Brief will be used to inform VA research activities and clinical care in the areas of mental health and substance use disorder treatment.

BACKGROUND

The term *psychedelics* refers to a group of substances that temporarily alter perception and mood and may impact numerous cognitive processes.[41,42] The term is used to describe naturally derived substances with these properties, such as psilocybin, as well as synthetic substances like lysergic acid diethylamide (LSD) and 3,4-methylenedioxymethamphetamine (MDMA).[43] Over time, various other terms have been used to describe and distinguish psychedelic substances including *hallucinogens*, *psychotomimetics*, *psycholytics*, and in the case of MDMA, *entactogens*.[44,45] For brevity, the term psychedelics is used in this report. Table 1 presents the derivation and proposed mechanism of selected psychedelic substances.

Naturally derived psychedelics have been used for millennia, often in the context of religious or spiritual practices. From the 1940s through the 1960s, psychedelics were studied in clinical research as potential treatments for a range of medical conditions including mood and substance use disorders. Despite some promising early findings,[46] research on psychedelic substances largely ceased in the US with passage of the 1970 Controlled Substances Act,[47] which codified psychedelics as drugs with no accepted medical use.[48] In recent years, a growing number of researchers have been revisiting the potential therapeutic benefits of psychedelics and have sought out legal and regulatory pathways to study them. Alongside renewed research interest, increasing media attention has raised public awareness of potential therapeutic uses of psychedelics. Although psychedelics are still categorized as Schedule I controlled substances, MDMA and psilocybin have received "breakthrough therapy" designation from the Food and Drug Administration (FDA) to be studied in adults with post-traumatic stress disorder (PTSD) and treatment-resistant depression, respectively.[49,50] In 2020, Oregon was the first state to create a regulatory framework for therapeutic psilocybin use,[51] with plans to allow psilocybin service centers with licensed facilitators to begin operating in 2023.

Most psychedelics used in research act as agonists or partial agonists at serotonin 5-hydroxytryptamine 2A receptors in the brain. This group includes LSD, psilocybin, and ayahuasca and are often referred to as classical psychedelics. In clinical contexts, classical psychedelics have most often been used to treat depression and substance use disorders. For these indications, it is thought that psychedelic use can disrupt problematic thought patterns and potentially lead to behavior change.[30] So-called non-classical psychedelics include MDMA and ibogaine. MDMA has most often been used to treat PSTD, as it is thought to reduce the anxiety and fear that can accompany memories of past trauma and thereby facilitate psychotherapy.[52]

MDMA works by complex mechanisms to promote release of serotonin, (nor)epinephrine, and dopamine and may stimulate signaling of oxytocin and other hormones. Ibogaine, used predominantly to treat substance use disorders, has a poorly understood mechanism of action but may work through a mix of neurotransmitters.[23] In general, psychedelics are intended to be used for therapeutic purposes once or a limited number of times and are not meant to be used as long-term treatment of mental health or substance use disorders.

Table 1. Characteristics of Selected Psychedelic Substances

Substance	Derivation	Proposed Mechanism of Action
Ayahuasca, a brewed drink containing N,N-dimethyltryptamine (N,N-DMT) and harmine, harmaline, and/or tetrahydroharmine	*Psychotria viridis* and *Banisteriopsis caapi*, plants indigenous to South America	Serotonin agonist (N,N-DMT) and monoamine oxidase inhibition (harmine, harmaline, and tetrahydroharmine)
5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT)	Venomous secretions of the Sonoran Desert/Colorado River toad and certain plant species	Serotonin agonist
Ibogaine	*Tabernanthe iboga* and *Voacanga africana, s*hrubs indigenous to West Africa	Poorly characterized; acts at multiple neurotransmitters
LSD (lysergic acid diethylamide)	First synthesized at Sandoz Laboratories (Switzerland) in 1943	Serotonin agonist
MDMA (3,4-methylenedioxymethamphetamine)	First synthesized at Merck Pharmaceuticals (Germany) in 1912	Promotes release of serotonin, (nor)epinephrine, and dopamine and may stimulate signaling of oxytocin and other hormones
Mescaline (3,4,5-trimethoxyphenethylamine)	Peyote cactus, San Pedro cactus, and other cacti species indigenous to North and South America	Serotonin agonist
Psilocybin	*Psilocybe* and other mushroom species, found worldwide	Serotonin agonist

The effectiveness of psychedelics is thought to in part depend on the treatment intentions of the patient and the physical environment in which psychedelics are administered ("set" and "setting," respectively).[53] In a clinical research setting, psychedelics are typically administered over a day-long dosing session in a monitored and controlled environment designed to promote relaxation and minimize disruption (*eg*, in a comfortable setting with the participant wearing eyeshades and listening to pre-selected music through headphones). In many cases, a specific number of structured psychotherapy sessions are delivered before and after psychedelic dosing. For example, treatment may involve 1–2 psychotherapy sessions before an extended 8–10-hour session in which the therapist or other health care personnel administers the psychedelic substance and monitors the participant for safety. The psychedelic session may then by followed by additional psychotherapy sessions to debrief and analyze the participant's psychedelic experience, often referred to as integration sessions. The cycle of psychedelic administration followed by post-psychedelic integration sessions may be repeated 2–3 times. Contemporary

studies of psychedelic substances have used different treatment protocols for a range of disorders and have employed study designs with differing research aims (*eg*, safety, feasibility, efficacy, effectiveness, comparative effectiveness).

Given the prevalence of mental health and substance use disorders within the Veteran population, any novel or emerging treatments with the potential to improve clinical outcomes are of great interest to VA patients, researchers, and other stakeholders.[54] Although VA services include comprehensive care for mental health and substance use disorders in a range of settings including residential rehabilitation,[55] a proportion of Veterans may not experience improvement with existing treatment options.[56] Therefore, psychedelics and psychedelic-assisted psychotherapy represent a potential new option for those with mental health or substance use disorders who have not responded to available treatments. The aim of this review is to inform VHA program planning by synthesizing available evidence on the benefits and harms of psychedelics as primary or adjunct treatment for mental health and substance use disorders.

METHODS

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42022330065).

KEY QUESTIONS

The following key questions (KQs) were the focus of this review:

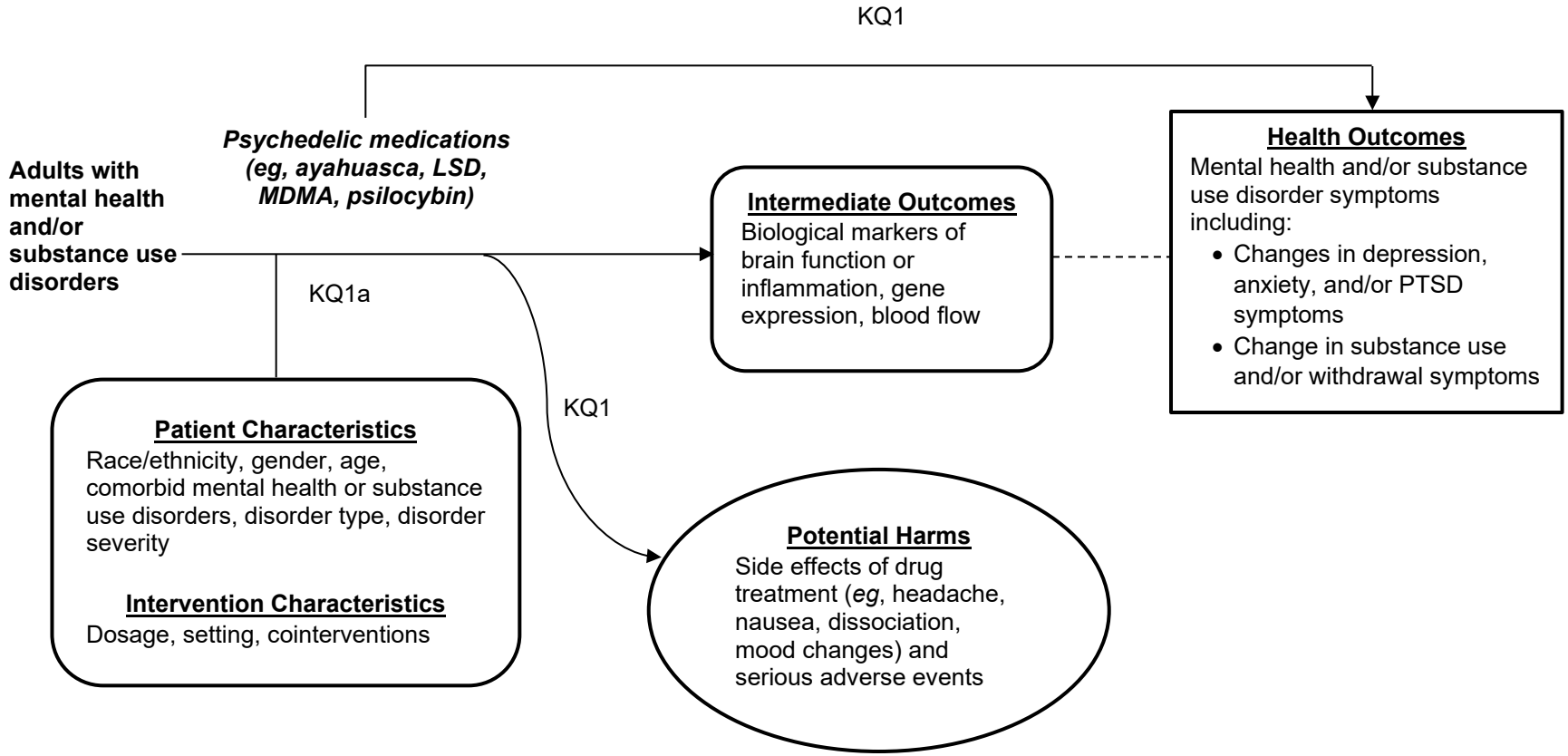
KQ1: What are the benefits and harms of psychedelic substances as primary or adjunct treatment for mental health and substance use disorders?

KQ1a: Do benefits or harms of psychedelic substances vary based on patient characteristics (*eg*, race/ethnicity, gender identity, age, comorbid mental health or substance use disorders, index trauma type), disorder type, or disorder severity?

ANALYTIC FRAMEWORK

The analytic framework shown in Figure 1 provides a conceptual overview of this review. The population of interest was adults with mental health and/or substance use disorders. Eligible outcomes included mental health and/or substance use disorder symptoms (Key Questions 1 and 1a) and treatment harms (Key Question 1). Whether benefits and/or risks of the intervention differ by patient characteristics (*eg*, patient demographics, comorbidities, disease severity) or treatment protocol (*eg*, number of sessions, dosage) was also of interest (Key Question 1a).

Figure 1. Analytic Framework



Abbreviations. LSD=lysergic acid; MDMA=3,4-methylenedioxymethamphetamine; PSTD=posttraumatic stress disorder.

ELIGIBILITY CRITERIA

The ESP included studies that met the following criteria:

***P**opulation*	Adults with mental health and/or substance use disorders (*eg*, depression, PTSD, opioid use disorder). Studies among adults with serious medical illness (*eg*, terminal cancer, end-stage renal disease) with mental health symptoms or substance use were excluded.
***I**ntervention*	Psychedelic substances (*eg*, ayahuasca/DMT, LSD, MDMA, psilocybin; excluding cannabinoids and ketamine) used as a primary treatment or as an adjunct to psychotherapy or another treatment (*ie*, psychedelic-assisted therapy)
***C**omparator*	Any (*eg*, placebo, treatment as usual)
***O**utcomes*	• Disorder symptoms • Quality of life/functioning • Harms (*eg*, treatment-emergent adverse events)
***S**tudy Design*	Systematic reviews, randomized controlled trials (RCTs), and concurrently controlled cohort studies. We considered longitudinal studies without comparison groups (*ie*, pre-post studies) and case series (*ie*, $N > 1$) only to address gaps in evidence from studies with control groups. We excluded case reports (*ie*, $N = 1$).

DATA SOURCES AND SEARCHES

To identify articles relevant to the key questions, a research librarian searched Ovid MEDLINE, Ovid PsycINFO, and ClinicalTrials.gov, as well as AHRQ, Cochrane Database of Systematic Reviews, and HSR&D through April 2022 using terms for *hallucinogen, psychedelic,* and *mental disorders* (see Appendix A in Supplemental Materials for complete search strategies). Additional citations were identified from hand-searching reference lists. We limited the search to published and indexed articles involving human subjects available in the English language. Study selection was based on the eligibility criteria described above. We excluded studies of cannabis and ketamine (a dissociative anesthetic) because these substances have distinct mechanisms of action compared to psychedelics and have been reviewed extensively elsewhere.[57-59] To ensure that study findings would be most applicable to contemporary diagnostic and management practices, we limited inclusion to studies published in 1994 or after to coincide with the publication of *Diagnostic and Statistical Manual of Mental Disorders-4*.[60]

Titles, abstracts, and full-text articles were independently reviewed by 2 investigators. All disagreements were resolved by consensus or discussion with a third investigator.

DATA ABSTRACTION AND ASSESSMENT

Effect information and population, intervention, and comparator characteristics were abstracted from all included studies. The internal validity (risk of bias) of each included study was rated using the Cochrane risk of bias tools.[61,62] All data abstraction and internal validity ratings were

first completed by 1 investigator and then checked by another; disagreements were resolved by consensus or discussion with a third investigator.

We graded the strength of the evidence for each outcome based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[63] This approach provides a rating of confidence in reported findings based on study methodology (design, quality, and risk of bias), consistency (whether effects are in the same direction and have a consistent magnitude), directness (whether assessed outcomes are clinically important to patients and providers), and precision of findings (*eg*, confidence intervals). For this review, we applied the following general algorithm: *high strength* evidence consisted of multiple, large trials with low risk of bias, consistent and precise findings, and clinically relevant outcomes; *moderate strength* evidence consisted of multiple trials with low to unclear risk of bias, consistent and precise findings, and clinically relevant outcomes; *low strength* evidence consisted of a single trial or multiple small trials and/or multiple observational studies, with unclear to high risk of bias, consistent findings, and clinically relevant outcomes; and *insufficient* evidence consisted of a single or multiple small observational studies with unclear or high risk of bias, or no available studies.

SYNTHESIS

We grouped studies by disorder and psychedelic type and described mean changes in symptoms, when possible including whether the psychedelic intervention led to a clinically meaningful improvement in symptom severity (as defined by the study) or disease remission. We focused synthesis on disorder-specific outcomes (*eg,* PTSD symptom severity) and did not describe outcomes related to the psychedelic experience itself or measures of mood or perception not directly relevant to the disorder being treated.

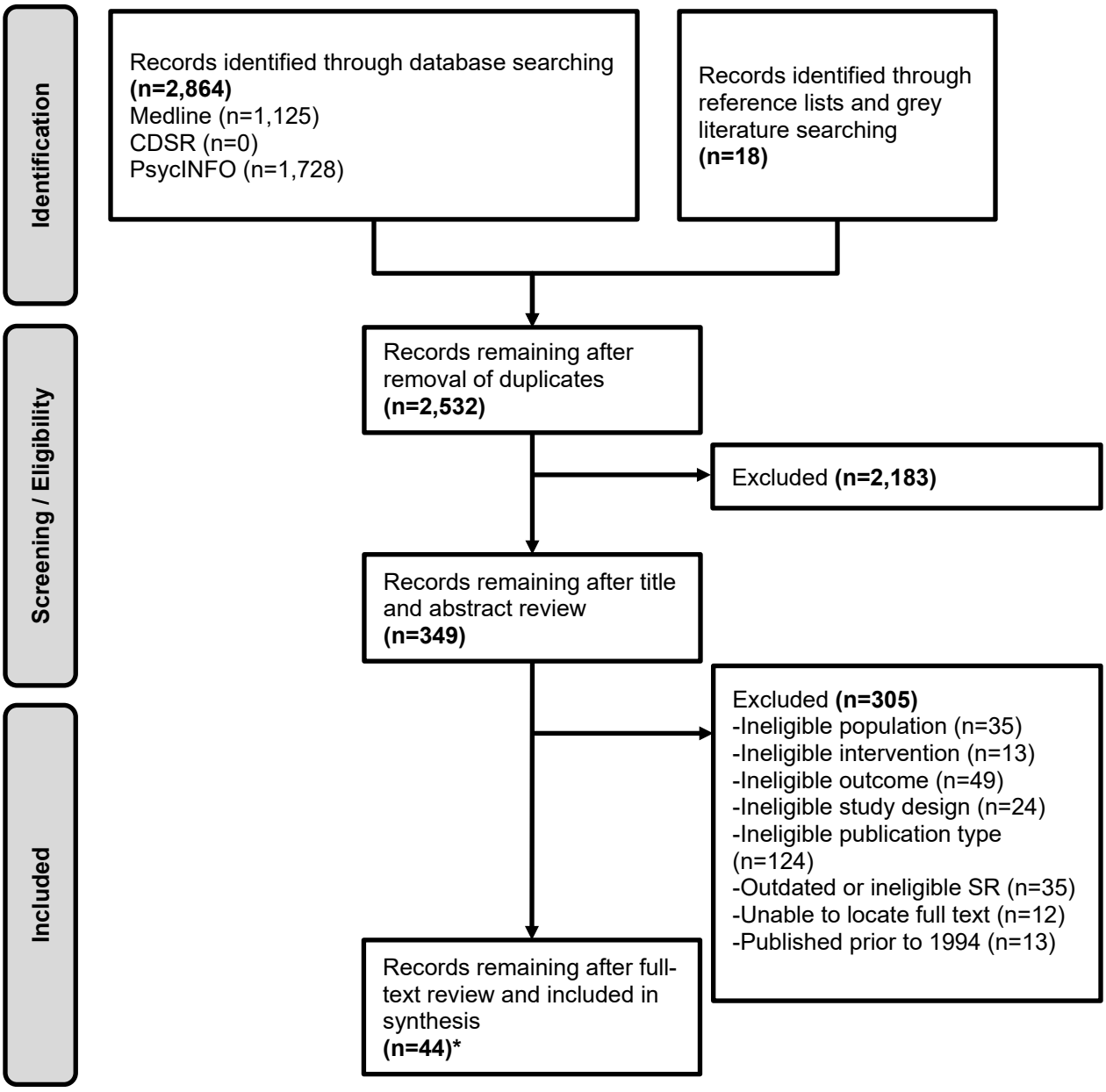
Trials of MDMA-assisted psychotherapy for PTSD used the Clinician-Administered PTSD Scale (CAPS) total severity score (CAPS-4 or CAPS-5, rated 0-136 or 0-80, respectively) to report mean changes in PTSD symptom severity from baseline for intervention and comparator groups. For these trials, we synthesized bias-adjusted standardized mean differences (SMDs; Hedges' *g*) in CAPS change scores between groups using random-effects meta-analysis. Precision of study-level and pooled mean differences is reported using 95% confidence intervals (CIs), which were also used to evaluate statistical significance at a significance level of .05. Heterogeneity in true study effects was estimated using restricted maximum-likelihood estimation and is presented as 95% prediction intervals (PIs). A PI encompassing values that substantively differ in direction and/or magnitude from the pooled MD indicates the presence of considerable heterogeneity.[64,65] The Hartung-Knapp-Sidik-Jonkman method was used to better account for uncertainty in estimating the amount of heterogeneity.[66] Meta-analyses were conducted using the *metafor*[67] package for R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 2) summarizes the results of the study selection process (a full list of excluded studies is available in Appendix B in Supplemental Materials).

Figure 2. Literature Flowchart



Notes. 38 studies in 44 publications.
Abbreviations. CDSR=Cochrane Database of Systematic Reviews; SR=systematic review.

LITERATURE OVERVIEW

Our search identified 2,532 potentially relevant articles. We included 38 studies (in 44 publications),[1-36,38-40,68-71] which are summarized in Table 2. Additional study details are provided in each section below and in Appendix C in the Supplemental Materials. Fifteen studies were RCTs, 21 were pre-post studies, and 2 were cohorts compared to healthy, non-treated controls. Participants included adults with PTSD, depression, obsessive compulsive disorder (OCD), social anxiety, opioid use disorder (OUD), alcohol use disorder, tobacco use, and mixed substance use disorders and mood symptoms. In most cases, studies described participants as having moderate to severe disease who had not improved with past treatment trials (more detail is provided in each section below). Adults with a personal or family history of a psychotic disorder or bipolar I disorder were generally excluded from study participation, as were those with major medical comorbidities and pregnant individuals. Studies inconsistently reported whether participants had previously used psychedelics; in some cases, recent or past use was a reason for exclusion. Sample sizes ranged from 3–191; the largest study[37] (N = 191) was of adults seeking treatment for opioid or cocaine dependence with ibogaine.

Most studies (61%) were conducted exclusively outside the US, with Brazil and the United Kingdom being the most common locations. However, most studies did not report whether participants were local to the region or had travelled there for treatment purposes. Given the legal restrictions on psychedelic use in many locations, it is likely that some studies included participants from multiple countries. Participant mean age ranged from 25 to 51 in studies reporting this information. Among studies conducted completely or partially in the US, most participants were non-Hispanic white. Only 1 study exclusively enrolled US Veterans: a pre-post study of 51 Special Operations Forces Veterans who were treated for a range of mood symptoms with ibogaine and 5-MeO-DMT during a 3-day residential program in Mexico.[40] Three studies of MDMA-assisted psychotherapy for PTSD included Veterans (range: 14–85% of total sample).[1,2,11]

MDMA was the only psychedelic used in studies of adults with PTSD. Psilocybin and ayahuasca were used most often in studies of adults with depression or substance use. Ibogaine was used in studies of adults with OUD and mixed substance use disorders. No studies of LSD published after 1994 met our inclusion criteria. Most studies of MDMA and psilocybin included intensive psychotherapy as a co-intervention. In contrast, most studies of ayahuasca and ibogaine did not include a therapy co-intervention. Comparators in RCTs included 0mg placebo, low-dose placebo (a lower dose of the same psychedelic used in the intervention group), or another non-psychedelic medication (*eg*, escitalopram, diphenhydramine). Most studies of PTSD required participants to discontinue usual mental health treatments except for sedative hypnotics or anxiolytics used between MDMA sessions (2 trials did not clearly report whether discontinuation was required). In most studies of depression, participants were not on other medical treatments for depression or were required to discontinue their usual treatments (usually antidepressant medications including selective serotonin reuptake inhibitors) for at least 2 weeks prior to the study period. Detail on whether studies did or did not require participants to discontinue their usual treatment are in Appendix C of the Supplemental Materials.

Most trials of MDMA for PTSD and psilocybin for depression were designed to evaluate treatment efficacy, while studies of ayahuasca and ibogaine were more often designed to evaluate safety and feasibility. Common methodological limitations of RCTs were small sample

sizes, unclear intervention adherence, and unclear handling and/or extent of missing data. Observational studies, which mostly used a pre-post design, were limited by the potential for selection bias and lack of control groups.

We identified 70 in-progress studies (see Appendix E in Supplemental Materials) examining psychedelic use in populations with mood disorders, anxiety disorders, and substance use disorders.

Table 2. Characteristics of Included Studies by Treatment Indication

Study	Location(s)	Study Design	Sample Size	Follow-up	Psychedelic(s)	Co-Intervention(s)	Comparator(s)	Risk of Bias Rating[a]
PTSD								
Bouso 2008[69]	Spain	RCT	6	12 months	MDMA	Psychotherapy	0mg placebo	High
Mitchell 2021[1]	US, Canada, & Israel	RCT	90	18 weeks	MDMA	Psychotherapy	0mg placebo	Some concerns
Mithoefer 2011[3] Mithoefer 2013[8]	US, Canada, & Israel	RCT	20	2 months – mean 45 months	MDMA	Psychotherapy	0mg placebo	Some concerns
Mithoefer 2018[2]	US	RCT	26	1 month	MDMA	Psychotherapy	Low-dose placebo	Low
Mithoefer 2019[68b]	US, Canada, Switzerland, & Israel	RCT	105	1–2 months	MDMA	Psychotherapy	0mg or low-dose placebo	Low
Oehen 2013[5]	Switzerland	RCT	12	12 months	MDMA	Psychotherapy	Low-dose placebo	Some concerns
Ot'alora 2018[4]	US	RCT	28	1 month	MDMA	Psychotherapy	Low-dose placebo	Some concerns
NCT01689740[6]	Israel	RCT	8	1 month	MDMA	Psychotherapy	Low-dose placebo	Not rated
NCT01958593[7]	Canada	RCT	6	1 month	MDMA	Psychotherapy	0mg placebo	Not rated
Jardim 2021[9]	Brazil	Pre-post	3	2 months	MDMA	Psychotherapy	NA	High
Monson 2020[10]	US & Canada	Pre-post	12	6 months	MDMA	Psychotherapy	NA	High
Wang 2021[11]	US & Canada	Pre-post	37	18 weeks	MDMA	Psychotherapy	NA	High
Major Depressive Disorder								
Carhart-Harris 2021[17]	UK	RCT	59	6 weeks	Psilocybin	Psychotherapy	Low-dose placebo and escitalopram	Some concerns
Davis 2021[12] Gukasyan 2022[70]	US	RCT	24	12 months	Psilocybin	Psychotherapy	Delayed treatment (wait list control)	Low

Study	Location(s)	Study Design	Sample Size	Follow-up	Psychedelic(s)	Co-Intervention(s)	Comparator(s)	Risk of Bias Rating[a]
Palhano-Fontes 2019[18] Zeifman 2021[22]	Brazil	RCT	29	1 week	Ayahuasca	None	0mg placebo	Some concerns
Carhart-Harris 2016[13] Carhart-Harris 2018[14]	UK	Pre-post	20	6 months	Psilocybin	Psychotherapy	NA	High
Lyons 2018[15]	UK	Cohort	30	1 week	Psilocybin	Psychotherapy	Healthy, non-treated controls	High
Stroud 2018[16]	UK	Cohort	32	1 month	Psilocybin	Psychotherapy	Healthy, non-treated controls	High
Osorio 2015[20]	Brazil	Pre-post	6	21 days	Ayahuasca	None	NA	High
Sanches 2016[19] Zeifman 2021[22]	Brazil	Pre-post	17	21 days	Ayahuasca	None	NA	High
Opioid Use								
Glue 2016[23]	New Zealand	RCT	27	~9 days	Noribogaine[c]	None	0mg placebo	Some concerns
Brown 2018[24]	Mexico	Pre-post	30	12 months	Ibogaine	None	NA	High
Davis 2017[25]	Mexico	Pre-post	88	3 months-3 years	Ibogaine	Detoxification program	NA	High
Knuijver 2022[27]	The Netherlands	Pre-post	14	24 hours	Ibogaine	None	NA	High
Malcolm 2018[28]	Mexico	Pre-post	50	48 hours	Ibogaine	Detoxification program	NA	Unclear
Noller 2018[26]	New Zealand	Pre-post	14	12 months	Ibogaine	Diazepam and zopiclone	NA	High
Alcohol Use								
Bogenschutz 2022[29]	US	RCT	95	36 weeks	Psilocybin	Psychotherapy	Diphenhydramine	Low

Study	Location(s)	Study Design	Sample Size	Follow-up	Psychedelic(s)	Co-Intervention(s)	Comparator(s)	Risk of Bias Rating[a]
Bogenschutz 2015[30]	US	Pre-post	10	36 weeks	Psilocybin	Psychotherapy	NA	High
Sessa 2021[31]	UK	Pre-post	14	9 months	MDMA	Psychotherapy	NA	High
Tobacco Use								
Johnson 2014[32] Johnson 2017[33]	US	Pre-post	15	6-16 months	Psilocybin	Psychotherapy	NA	High
Cocaine and Cannabis Use								
Thomas 2013[34]	Canada	Pre-post	12	6 months	Ayahuasca	Participation in 4-day retreat	NA	High
Mash 2018[37]	St. Kitts	Pre-post	191	1 month	Ibogaine	Inpatient detoxification program	NA	High
Mash 2001[71]	St. Kitts	Pre-post	32	36 hours-10 days	Ibogaine	Inpatient detoxification program	NA	High
Mash 2000[36]	St. Kitts	Pre-post	27	1 month	Ibogaine	Inpatient detoxification program	NA	High
Schenberg 2014[35]	Brazil	Pre-post	75	NR	Ibogaine	Psychotherapy	NA	High
Other Conditions								
Davis 2020[40]	Mexico	Pre-post	51	1 month-2 years	Ibogaine 5-MeO-DMT	Group therapy	NA	High
Dos Santos 2021[38]	Brazil	RCT	17	3 weeks	Ayahuasca	None	0mg placebo	Some concerns
Moreno 2006[39]	US	Pre-post	17	3 weeks	Psilocybin	None	NA	High

Notes. [a] Full details of quality assessments are in Appendix C of Supplemental Materials; [b] Pooled analysis of 6 studies: Mithoefer 2011, Mithoefer 2018, Oehen 2013, Otalora 2018, NCT01958593, and NCT01689740; [c] Ibogaine active metabolite.
Abbreviations. PTSD=posttraumatic stress disorder; RCT=randomized controlled trial; UK=United Kingdom; US=United States.

POSTTRAUMATIC STRESS DISORDER

In a clinical research setting, MDMA-assisted psychotherapy may reduce PTSD symptoms, resulting in a clinically meaningful improvement (defined as a reduction in CAPS score by at least 30%) and/or disease remission in the short term (1 month to 18 weeks). We have low confidence in these findings based on several small trials with consistent and direct results with some imprecision (wide confidence intervals). Few serious adverse events were reported across studies, and only 1 event was ultimately attributed to MDMA.

We identified 7 unique RCTs[1-7] of MDMA-assisted psychotherapy compared to psychotherapy with a 0mg placebo or low-dose placebo, and 1 RCT[68] that pooled results from 6 of these trials. Studies used the CAPS total severity score (CAPS-4 or CAPS-5, rated 0–136 or 0–80, respectively) to report mean change from baseline in PTSD symptom severity for intervention and comparator groups. CAPS is conducted by a semi-structured interview that accesses an individual's trauma history as defined by the *Diagnostic and Statistical Manual of Mental Disorders*. All studies included participants with moderate (total severity score 40–59 on CAPS-4[72] and 23–34 on CAPS-5[1]) or severe (≥60 on CAPS-4 and ≥35 on CAPS-5) symptoms at baseline (Table 3). Most studies included participants who had been experiencing PTSD symptoms for years and had previously undergone at least 1 medication or psychotherapy trial.

Participants assigned to intervention groups received MDMA 80–125mg with or without a 40–62.5mg supplemental dose. Three studies used a 0mg placebo, and 4 studies used a low-dose placebo (MDMA 25–40mg with or without a 15mg supplemental dose). Low-dose placebos were intended to maintain participant blinding by producing some sensations of having ingested a psychedelic but without the same therapeutic psychedelic effect as the active treatment dose. Intervention and control group participants underwent the same intensive psychotherapy protocol, which typically consisted of 2–3 preparatory sessions, 2–3 MDMA or placebo dosing sessions, and 4–6 follow-up sessions (integration sessions) which were all co-led by 2 mental health professionals. More information regarding the MDMA dosing sessions is available in Appendix C of the Supplemental Materials. All trials were conducted by researchers affiliated with the Multidisciplinary Association for Psychedelic Studies (MAPS) or were sponsored by this organization and all reported using the same standardized manual to guide psychotherapy sessions (publicly available at http://maps.org/treatment-manual). No study compared MDMA-assisted psychotherapy to another active treatment (*ie*, psychotherapy paired with a different psychedelic at therapeutic dosages) or to no treatment. Follow-up duration in most trials was 1–2 months.

Table 3. Psychedelic-assisted Psychotherapy for PTSD: Study Characteristics

Study ***Sample Size***[a]	**Patient Characteristics**	**Mean (SD) CAPS Baseline**[b]	**Mean (SD) Symptom Duration**	**Past Treatment(s)**	**Psychedelic** ***Dose***	**Psychotherapy Protocol**[c] ***Total Number of Sessions and Duration (Hours)***	**Comparator**
RCTs							
Bouso, 2008[69d] N=6	Mean age: 36 % female: 100 % non-Hispanic White: 0%	NR	NR	At least 1 standard treatment (not further defined)	MDMA *50–75mg, 1 dosing session*	3 90-min sessions before and after a single 8-hour MDMA session *7 sessions (17 hours)*	0mg placebo
Mitchell, 2021[1] N=79	Mean age: 41 % female: 66 % non-Hispanic White: 90	CAPS-5: 44.1 (6.04)	14 (12) years	NR	MDMA *Session 1: 120mg Sessions 2-3: 180mg*	3 90-min preparatory sessions, 3 8-hour MDMA sessions, and 9 90-min integration sessions *15 sessions (42 hours)*	0mg placebo
Mithoefer, 2011[3] & Mithoefer, 2013[8] N=20	Mean age: 40 % female: 85 % non-Hispanic White: 100	CAPS-4: 79.4 (22.4)	248 (173) months	At least 1 pharmacotherapy or psychotherapy	MDMA *Sessions 1-2: 125mg ±supplemental 62.5mg*	2 90-min preparatory sessions, 2 all-day MDMA sessions and overnight clinic stays, 8 90-min integration sessions *12 sessions (~35 hours)*	0mg placebo
Mithoefer, 2018[2] N=19	Mean age: 37 % female: 27 % non-Hispanic White: 85	CAPS-4: 87.1 (16.4)[e]	85 (64) months	At least 3 months of SSRI or SNRI treatment and 6 months of psychotherapy	MDMA *Sessions 1-2: 75mg or 125mg ± supplemental half-dose*	3 90-min preparatory sessions, 2 8-hour MDMA sessions and overnight clinic stays, 6 90-min integration sessions *11 sessions (34-42 hours)*	Low-dose placebo
Mithoefer 2019[68f] N=105	Mean age: 41 % female: 61 % non-Hispanic White: 92	CAPS-4: 84.5 (18.4)	215.3 (190) months	Pharmacotherapy or psychotherapy	MDMA *Sessions 1-2: 75mg, 100mg, or 125 mg*	2-3 90-min preparatory sessions, 2 8-hour MDMA sessions and overnight clinic stays, and 3-4 90-min integration sessions *7–9 sessions (24–27 hours)*	0mg or low-dose placebo
Oehen, 2013[5] N=12	Mean age: 41 % female: 83 Race/ethnicity NR	CAPS-4: 65.4 (11.7)[e]	18.3 (12) years	At least 3 months of SSRI treatment and 6 months of psychotherapy	MDMA *Sessions 1-3: 125mg + 62.5mg supplemental dose*	3 preparatory sessions, 3 8-hour MDMA sessions and overnight clinic stays, 12 integration sessions *18 sessions (NR)*	Low-dose placebo

Study ***Sample Size***[a]	**Patient Characteristics**	**Mean (SD) CAPS Baseline**[b]	**Mean (SD) Symptom Duration**	**Past Treatment(s)**	**Psychedelic** ***Dose***	**Psychotherapy Protocol**[c] ***Total Number of Sessions and Duration (Hours)***	**Comparator**
Ot'alora, 2018[4] N=18	Mean age: 42 % female: 68 % non-Hispanic White: 93	CAPS-4: 91.9 (17.4)[e]	353 (232) months	At least 1 pharmacotherapy or psychotherapy	MDMA *Sessions 1-2: 100 or 125mg*	3 90-min preparatory sessions, 2 8-hour MDMA sessions, and 6 integration sessions *10 sessions (NR)*	Low-dose placebo
NCT01689740[6] N=8	Mean age: NR % female: 38 % non-Hispanic White: 87	Moderate-severe (CAPS NR)	>6 months	NR	MDMA *Sessions 1-2: 125mg + 62.5mg supplemental dose*	3 preparatory sessions, 2 MDMA sessions, and 2 integration sessions *7 sessions (NR)*	Low-dose placebo
NCT01958593[7] N=6	Mean age: 48 % female: 50 % non-Hispanic White: 83	Moderate-severe (CAPS NR)	>6 months	NR	MDMA *Sessions 1-2: dose NR*	3 preparatory sessions, 2 MDMA sessions, and 2 integrative therapy sessions *7 sessions (NR)*	0mg placebo
Observational Studies							
Jardim, 2021[9] N=3	Mean age: 40 % female: 67 % non-Hispanic White: 67	CAPS-4: 80 (7.5)[e]	NR	At least 1 pharmacotherapy or psychotherapy	MDMA *Session 1 :112.5mg* *Sessions 2-3: 187.5mg*	3 90-min preparatory sessions, 3 8-hour MDMA sessions, and 9 90-min integrative therapy sessions *15 sessions (42 hours)*	None

Study ***Sample Size***[a]	**Patient Characteristics**	**Mean (SD) CAPS Baseline**[b]	**Mean (SD) Symptom Duration**	**Past Treatment(s)**	**Psychedelic** ***Dose***	**Psychotherapy Protocol**[c] ***Total Number of Sessions and Duration (Hours)***	**Comparator**
Monson, 2020[10] N=12 (6 couples)	Mean age: 47 % female: 50 % non-Hispanic White: 100	CAPS-5: 41.42 (5.76)	NR	Pharmacotherapy or psychotherapy	MDMA *Session 1: 75mg* *Session 2: 100mg second session ±suppl. half-dose*	5 preparatory CBCT sessions, 2 MDMA 6–8 hour MDMA sessions, 2 1.25 hour integration sessions, 8 post MDMA CBCT sessions *19 sessions (NR)*	None
Wang, 2021[11] N=37	Mean age: 36 % female: 60 % non-Hispanic White: 73	CAPS-5: 45.4 (7.2)	*10 (11) years*	Antidepressant (73%) or psychotherapy (52%)	MDMA *120–150mg in divided doses; 3 dosing sessions*	3 preparatory sessions, 3 6–8-hour MDMA sessions and overnight clinic stays, and 9 integration sessions *15 sessions (NR)*	None

Notes. [a] Analytic sample; [b] CAPS total severity score, range for CAPS-4 0-136 and range for CAPS-5 0-80; [c] All sessions led by 2 co-therapists; Manualized therapy was conducted in accordance with the MDMA-assisted therapy treatment manual (http://maps.org/treatment-manual) unless otherwise specified. [d] Study terminated early and not included in overall SOE rating; [e] Weighted means calculated across intervention/comparator groups; [f] Pooled analysis of 6 studies: Mithoefer 2011, Mithoefer 2018, Oehen 2013, Otalora 2018, NCT01958593, and NCT01689740.
Abbreviations. CAPS=Clinician Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders; CBCT=cognitive behavioral conjoint therapy; MDMA=3,4-methylenedioxy-methamphetamine; NR=not reported; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin and norepinephrine reuptake inhibitor; UK=United Kingdom; US=United States.

Although all available trials reported mean changes in CAPS total severity scores, only 5 also reported the proportion of participants who no longer met criteria for PTSD (*ie*, experienced disease remission) or the proportion who experienced a clinically meaningful improvement in symptoms (defined as ≥30% decrease in CAPS total severity score compared to baseline). Across these 5 trials,[1-5] a higher proportion of participants who received MDMA-assisted psychotherapy experienced PTSD remission and/or at least a 30% decrease in CAPS scores compared to comparison group participants (Table 4).

Table 4. Effects of MDMA-assisted Psychotherapy on PTSD Diagnosis and Clinically Meaningful Improvement in CAPS Total Severity Score

Study *Follow-up*	N[a]	Intervention and Comparator	PTSD Outcome Measures
Mitchell, 2021[1] *18 weeks*	79	MDMA-assisted psychotherapy compared to 0mg placebo	Participants no longer meeting PTSD diagnostic criteria = 33% MDMA group vs 5% placebo group
Mithoefer, 2011[3] *2 months*	20	MDMA-assisted psychotherapy compared to 0mg placebo	Participants no longer meeting PTSD diagnostic criteria = 83% MDMA group vs 25% placebo group CAPS response[b] = 83% MDMA group vs 25% placebo group
Mithoefer, 2018[2] *1 month*	19	MDMA-assisted psychotherapy compared to low-dose placebo	Participants no longer meeting PTSD diagnostic criteria = 86% 75mg MDMA group and 58% 125mg MDMA group vs 29% control group CAPS response[b] = 100% 75mg MDMA group and 67% 125mg MDMA group vs 29% control group
Oehen, 2013[5] *2 months*	12	MDMA-assisted psychotherapy compared to low-dose placebo	CAPS response[b] after all participants received full-dose MDMA = 75%
Ot'alora, 2018[4] *1 month*	18	MDMA-assisted psychotherapy compared to low-dose placebo	Participants no longer meeting PTSD diagnostic criteria = 44% 100mg MDMA group and 42% 125mg MDMA group vs 33% control group CAPS response[b] = 56% 100mg MDMA group and 50% 125mg MDMA group vs 17% control group

Notes. [a] Analytic sample; [b] Response was defined as >30% decrease in CAPS total severity score.
Abbreviations. CAPS=Clinician Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders; MDMA=3,4-methylenedioxy-methamphetamine; PTSD=posttraumatic stress disorder.

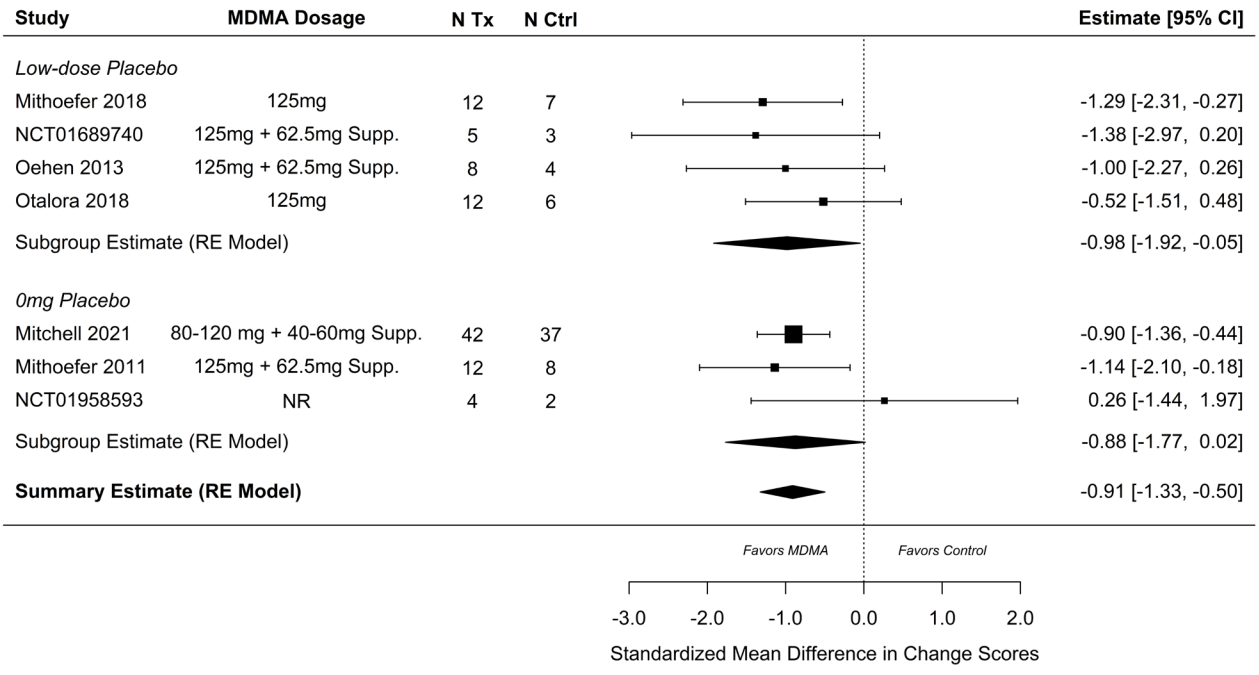
Results of a meta-analysis of 7 trials (Figure 3) indicate that participants receiving MDMA experienced significantly greater improvements in mean CAPS total severity scores compared with participants receiving 0mg or low-dose placebo (pooled standardized mean difference in change scores = -0.91, 95% CI [-1.33, -0.50]). Heterogeneity in true effects appeared to be minimal (95% PI [-1.33, -0.50]). No studies stratified results by patient characteristics or PTSD severity at baseline. These findings are consistent with results of a small RCT[69] conducted in Brazil that used a different assessment of PTSD symptomatology (Severity of Symptoms Scale for Post-traumatic Stress Disorder) and was terminated early due to reasons unrelated to trial conduct, as well as 3 observational studies.[9-11]

Across most studies, control group participants also experienced symptom improvements regardless of the type of placebo used, although to a lesser degree than treatment group

participants (median standardized symptom change of -0.90 and -1.54, respectively). Because both treatment and control group participants received psychotherapy in all studies, this observation suggests that treatment benefits are at least partially attributable to MDMA. Nonetheless, the small number and size of available studies limits the extent to which firm conclusions can be drawn about the relative contributions of receiving MDMA, undergoing intensive psychotherapy, and other factors (such as participation effects) to observed symptom improvement.

Additionally, the precise magnitude of benefit that could be expected from MDMA is difficult to determine from the available evidence, in part because very small RCTs are at risk of prognostic imbalance (a failure of randomization to balance groups on participants' responsiveness to treatment). The largest available RCT[1] is less likely to be impacted by this bias, and provides an estimate of added treatment benefit due to MDMA that corresponds to an approximately 5 to 15-point greater reduction in PTSD symptom severity compared to psychotherapy only (unstandardized mean difference in CAPS-5 change scores = -10.5, 95% CI [-15.6, -5.4]). Like 2 other studies, however, this study used a 0mg placebo, which likely compromised participant blinding and may have led to biases in observed treatment effects.

Figure 3. Change in Total CAPS Score Following MDMA-assisted Psychotherapy Compared to 0mg Placebo or Low-dose Placebo



Abbreviations. Ctrl=control group; NR=not reported; Supp=supplemental dosage; RE=random-effects model; Tx=treatment group.

MAJOR DEPRESSIVE DISORDER

Psilocybin-assisted psychotherapy may reduce depression severity and lead to a clinically significant improvement or sustained remission for some recipients at 12 months. Ayahuasca use may be associated with a short-term reduction in mean depression symptom scores and suicidality. Our confidence in these findings is low given study methodological limitations,

inconsistency, and small sample sizes. No serious adverse events were reported for either intervention.

We identified 2 small RCTs[12,17] of psilocybin-assisted psychotherapy and 3 small observational studies[13-16] in participants with moderate to severe depression (Table 5). The intervention in both trials consisted of 2 doses of psilocybin 20–30mg paired with pre-and post-treatment psychotherapy sessions led by 2 mental health professionals. In 1 of the trials,[12] conducted in the US among 24 adults with depression symptoms for a mean of 22 years, outcomes among the intervention group were compared to wait list controls who underwent the same treatment 8 weeks later. At baseline, participants had moderate depression according to the GRID-Hamilton Depression Rating Scale (GRID-HAMD; rated as no depression (0–7), mild depression (8–16), moderate depression (17–23), or severe depression (≥24)). If participants were taking antidepressants, they were required to refrain from using them prior to study screening and through completion of the primary outcome assessment but could start or restart antidepressant medication afterward. At 4-week and 3-, 6-, and 12-month follow-up, respectively, 0 (0%), 3 (12.5%), 5 (20.8%), and 8 (33.3%) of participants reported antidepressant use. Participants were allowed to continue psychotherapy throughout the trial if the type and frequency of psychotherapy had been stable and was expected to remain stable. At 4-week and 3-, 6-, and 12-month follow-up, respectively, 8 (33.3%), 9 (37.5%), 10 (41.7%), and 10 (41.7%) of participants reported receiving psychotherapy since receiving psilocybin.

Depression symptoms as measured by the GRID-HAMD significantly improved at 8 weeks compared to the delayed treatment group (standardized mean difference [SMD] = 2.6, 95% CI [1.5, 3.7]). In the immediate treatment group, the mean (SD) GRID-HAMD scores were 22.9 (3.6) at baseline, 8.0 (7.1) at week 5, and 8.5 (5.7) at week 8. Scores in the delayed treatment group remained stable: 22.5 (4.4) at baseline, 23.8 (5.4) at week 5, and 23.5 (6.0) at week 8. At 12 months, improvement on GRID-HAMD for all participants (immediate and delayed treatment groups) was also significant (SMD = 2.4, 95% CI [1.6, 3.2]).[70] At 12 months, 18/24 (75%) of participants experienced a clinically significant response, which was defined by the study as a decrease of 50% or more from their pre-treatment GRID-HAMD total score, and 14/24 (58%) met criteria for disease remission, defined as a GRID-HAMD total score of 7 or lower. GRID-HAMD scores at 12 months were not significantly different among participants who reported receiving psychotherapy during the follow-up period (the same analysis was not reported for antidepressant use). Suicidal ideation as measured by the Columbia Suicide Severity Rating Scale (CSSRS) severity of ideation subscale (score range of 0–5,with higher scores indicating presence of ideation with at least some intent to die) was 1.2 (1.2), 0.3 (0.7), 0.2 (0.7), 0.5 (1.0), 0.6 (1.1), 0.6 (1.1), respectively, at baseline, 1-week, 4-week and 3-, 6-, and 12-month follow-up (N = 23 due to missing data). No serious adverse events were reported and there were no reported suicide attempts or instances of self-harm at 12 months. The trial did not stratify results by patient characteristics or disease severity.

In a second trial[17] of psilocybin-assisted psychotherapy conducted in the UK that included 59 adults, the comparison group was treated with a low-dose placebo (psilocybin 1mg, presumed to have negligible activity) and escitalopram 10-20mg daily. The primary outcome measure was change from baseline scores on the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16; rated as no depression (0–5), mild depression (6–10), moderate depression (11–15), severe depression (16–20), or very severe depression (21–27)). At baseline, participants in the psilocybin group (N = 30) and escitalopram groups (N = 29), respectively, had mean QIDS-

SR-16 scores (SD, range) of 14.5 (3.9; 7–23) and 16.4 (4.1; 6–22). Psilocybin group participants had depression for a mean of 22 years, had previously tried an average of 2 psychiatric medications, and 93% had previously undergone psychotherapy. Escitalopram group participants had depression for a mean of 15 years, had tried an average of 2 psychiatric medications, and 90% had previously undergone psychotherapy. Alcohol use was more common in the escitalopram group (average weekly use of 68 grams compared to 37 grams). Participants were required to stop any use of psychiatric medication at least 2 weeks before starting the trial and stop psychotherapy at least 3 weeks beforehand.

Both the psilocybin and escitalopram groups had reductions in mean QIDS-SR-16 scores. However, the change in mean scores from baseline to week 6 was not significantly different between the 2 groups (mean difference [MD] = -2.0, 95% CI [-5.0, 0.9]). A clinically meaningful response (defined as a decrease in QIDS-SR-16 by at least 50%) occurred in 21/30 (70%) of the psilocybin group and 14/29 (48%) in the escitalopram group. Remission (defined as QIDS-SR-16 score <5) occurred in 17/30 (57%) in the psilocybin group and 8/29 (28%) in the escitalopram group. Neither response nor remission rates were significantly different between groups (Table 5). Changes in suicidal ideation as measured by the Suicidal Ideation Attributes Scale (SIDAS) were also not significantly different. No serious adverse events occurred. The trial did not stratify results by patient characteristics or disease severity.

The same group of researchers who conducted the UK trial also published 4 small observational studies on an intervention consisting of 2 doses of psilocybin (10mg followed by 25mg) combined with psychological support before, during, and after psilocybin treatments.[13-16] The number of participants who were exposed to this intervention ranged from 12–20 in each study, but importantly, some participants overlapped between studies. Results consistently showed a reduction in depression severity (as measured by QIDS-16 and the Beck Depression Inventory) at 1–8 weeks following the intervention. In the study with the longest duration, the change in QIDS-SR-16 from baseline to 6 months among 20 participants was significant (within-group SMD = 1.4, $p < 0.001$).[14] These observational studies aimed to test the feasibility of studying psilocybin-assisted psychotherapy and explore associations of psilocybin use with factors related to depression such as future life event forecasting and emotional face recognition (both outcomes are outside the scope of this review). Although necessary to establish a basis for further study, results of these observational studies did not weigh heavily in our assessment of the evidence compared with findings from RCTs.

Table 5. Study Characteristics and Outcomes of Psilocybin-assisted Psychotherapy for Depression

Study ***Sample Size***	**Patient Characteristics**	**Mean (SD) Baseline Severity and Symptom Duration** ***Past Treatment***	**Psychedelic** ***Dose***	**Psychotherapy Protocol[a]** ***Total # Sessions and Duration (Hours)***	**Comparator**	**Outcomes**
RCTs						
Carhart-Harris 2021[17] N=59	Mean age: 41 % female: 34 % non-Hispanic White: 88	HAMD: 18.8 (2.8)[b] 19 (11) years *Average of 2 previous medication trials; 92% previously tried psychotherapy*	Psilocybin *Sessions 1-2: 25mg*	1 preparatory session, 2 dosing sessions, 3 debriefing sessions *6 sessions (NR)*	Psilocybin 1mg dosed twice and escitalopram 10–20mg daily	MD change in QIDS-SR-16 from baseline to week 6 = -2.0, 95% CI [−5.0, 0.9] 6-week QIDS-SR-16 response[c] 21/30 (70%) of the psilocybin group and 14/29 (48%) in the escitalopram group (difference, 22 percentage points; 95% CI [−3, 48]) 6-week remission[d] 17/30 (57%) in the psilocybin group and 8/29 (28%) in the escitalopram group (difference, 28.1 percentage points; 95% CI [2.3, 53.8]). MD change in SIDAS score from baseline to week 6 = -1.3, 95% CI [-6.5, -0.3]

Study ***Sample Size***	**Patient Characteristics**	**Mean (SD) Baseline Severity and Symptom Duration** ***Past Treatment***	**Psychedelic** ***Dose***	**Psychotherapy Protocol[a]** ***Total # Sessions and Duration (Hours)***	**Comparator**	**Outcomes**
Davis 2021[12] & Gukasyan 2022[70] N=24	Mean age: 40 % female: 67 % non-Hispanic White: 92	HAMD: 22.7 (4.0)[b] 22 (12) years *NR*	Psilocybin *Session 1: 20mg/70kg* *Session 2: 30mg/70 kg*	Preparatory visits (8 hrs total), support during 2 day-long psilocybin sessions, and follow-up visits (2–3 hrs total) *At least 18 in-person visits (~11 hours psychotherapy)*	Delayed treatment (wait list control)	SMD GRID-HAMD at 8 weeks (between group difference) = 2.6, 95% CI [1.5, 3.7] SMD GRID-HAMD at 12 months (all participants) = 2.4, 95% CI [1.6, 3.2] 12-month GRID-HAMD response[c] 18/24 (75%) 12-month remission[e] 14/24 (58%) CSSRS low overall and not significantly different between groups at 8 weeks
Observational Studies						
Carhart-Harris 2016[13] & 2018[14] N=20	Age: 27–64 % female: 30 % white: 75	HAMD: 21.5 (4.2) 18 (8) years *Psychotherapy (92%)*	Psilocybin *Session 1: 10mg Session 2: 25mg*	1 preparatory session (4 hrs), 2 dosing sessions (6–7 hrs each), and 2 integration sessions *5 sessions (NR)*	NA	SMD in QIDS-SR-16 from baseline to 6 months = 1.4, $p < 0.001$ MD in suicidality scores on QIDS-SR-16 from baseline to 5 weeks = -0.7, 95% CI [-0.22, -1.2] Relapse rate (QIDS score of 6+ or above) at 6 months among responders: 3/9 (33%)

Study ***Sample Size***	**Patient Characteristics**	**Mean (SD) Baseline Severity and Symptom Duration** ***Past Treatment***	**Psychedelic** ***Dose***	**Psychotherapy Protocol**[a] ***Total # Sessions and Duration (Hours)***	**Comparator**	**Outcomes**
Lyons 2018[15f] N=30	Mean age: 42 % female: 27 % non-Hispanic White: 93	BDI: 19.2 (1.5) NR	Psilocybin *Session 1: 10mg Session 2: 25mg*	1 preparatory session (4 hrs), 2 dosing sessions (6-7 hrs each), and 2 integration sessions *5 sessions (NR)*	Healthy, non-treated controls	Mean BDI = 34.33 at baseline vs 12.13 at 1 week among depressive patients ($p < 0.001$) No significant difference found in baseline vs follow-up BDI scores among the healthy comparison group.
Stroud 2018[16f] N=33	Mean age: 45 % female: 47 % non-Hispanic White: NR	QIDS: 11.7 (3.0)[b] NR	Psilocybin *Session 1: 10mg Session 2: 25mg*	1 preparatory session (4 hrs), 2 dosing sessions (6-7 hrs each), and 2 integration sessions *5 sessions (NR)*	Healthy, non-treated controls	Mean QIDS-16 = 18.88 at baseline vs 7.65 at 1 week after psilocybin sessions, ($p < .001$) No significant difference found in baseline vs follow-up QIDS-16 scores among the healthy comparison group

Notes. [a] All sessions led by 2 psychiatrists; [b] Weighted mean calculated across intervention and control groups; [c] Response defined by the study as a decrease of 50% or more from their pre-treatment total score; [d] Defined as <5 on QIDS-SR; [e] Defined as a GRID-HAMD total score of 7 or lower; [f] Intervention group also formed part of the sample in Carhart-Harris 2016 and Carhart-Harris 2018.
Abbreviations. BDI=Beck Depression Inventory; CI=confidence interval; CSSRS=Columbia Suicide Severity Rating Scale; GRID-HAMD=GRID-Hamilton Depression Rating Scale; HAM-D=Hamilton Rating Scale for Depression; MADRS= Montgomery-Asberg Depression Rating Scale; MD=mean difference; NR=not reported; QIDS-SR-16=16-item Quick Inventory of Depressive Symptomatology Self Report; RCT=randomized controlled trial; SD=standard deviation; SI=suicidal ideation; SMD=standardized mean difference; SIDAS=Suicidal Ideation Attributes Scale.

We identified 1 small RCT[18] ($N = 29$) on ayahuasca for treatment of depression and 2 small pre-post studies (Table 6). In the trial conducted in Brazil, participants had moderate to severe depression as defined by mean Hamilton Depression Rating (HAM-D; rated as mild (10–13), mild to moderate (14–17), or moderate to severe (>17)) with a mean (SD) baseline score of 21.83 (5.35), had tried at least 2 antidepressant medications, and most (80%) had previously tried psychotherapy. Participants in the intervention group received 1 dose of ayahuasca without additional co-interventions aside from supervision during the dosing session and follow-up study assessments. The control group received an 0mg placebo designed to mimic the taste and color of ayahuasca. Mean HAM-D scores 1 week after treatment were significantly different between groups and favored ayahuasca (SMD = 0.98, 95% CI [0.21, 1.75]). A higher proportion of participants in the ayahuasca group met criteria for a clinically meaningful response (reduction in HAM-D score by at least 50%) and remission (HAM-D ≤7) (Table 6). This trial did not follow participants longer than 1 week, so the durability of these responses is unknown. Suicidal ideation decreased in both groups, but between-group differences were not significant. It is notable that 76% of participants had a comorbid personality disorder, 31% had comorbid anxiety disorder, and all were under regular use of benzodiazepines during the trial. Whether these factors influenced results is unclear, and the trial did not stratify results by patient characteristics.

The same researchers who conducted this RCT also conducted 2 small observational studies[19,20,22] that identified similar reductions in depression symptom severity in the 3 weeks following use of ayahuasca by 23 adults with recurrent depression. Among 15 patients with suicidality at baseline, ayahuasca use was associated with a reduction in suicidality as measured by Montgomery-Åsberg Depression Rating Scale-Suicidality Item (MADRS-SI) in the acute period (up to 180 minutes after ayahuasca administration) and for the next 21 days. These observational studies contributed little to our assessment of the evidence given that RCT data are available. No serious adverse events were reported for any studies of ayahuasca.

Table 6. Study Characteristics and Outcomes of Ayshuasca for Depression

Study ***Sample Size***	**Patient Characteristics**	**Mean (SD) Baseline Severity** **Symptom Duration** ***Past Treatment***	**Psychedelic** ***Dose***	**Psychotherapy protocol** ***Total # Sessions and Duration (Hours)***	**Comparator**	**Depression Outcomes**
RCT						
Palhano-Fontes 2019[18] Zeifman 2021[22] N=29	Mean age: 42 % female: 72 % non-Hispanic White: 59	HAMD: 21.8 (4.9)[a] 11 (9) years *Past trials of 3.86 ± 1.66 antidepressants; 80% previously tried psychotherapy*	Ayahuasca *1 ml.kg containing 0.36 mg/kg N, N-DMT, 1 dosing session*	1 dosing session supported by 2 facilitators with debriefing immediately after dosing session *1 session (8 hours)*	0mg placebo	SMD HAM-D at 1 week = 0.98, 95% CI [0.21, 1.75] 1-week HAM-D response[b] 8/14 (57%) of ayahuasca group and 3/15 (20%) in the placebo group (OR = 5.33, 95% CI [1.11, 22.58]) 1-week remission[b] 6/14 (43%) in the ayahuasca group and 2/15 (13%) in the placebo group (OR = 4.87, 95% CI [0.77, 26.73]) Suicidal ideation (MADRS-SI) decreased over time (p < 0.05), but was not different between ayahuasca and placebo groups (p = 0.088).

Study ***Sample Size***	**Patient Characteristics**	**Mean (SD) Baseline Severity** **Symptom Duration** ***Past Treatment***	**Psychedelic** ***Dose***	**Psychotherapy protocol** ***Total # Sessions and Duration (Hours)***	**Comparator**	**Depression Outcomes**
Observational Studies						
Osorio 2015[20] N=6	Mean age: 44 % female: 67 % non-Hispanic White: NR	HAMD: 17.2 (7.1)[a] NR	Ayahuasca *120–200ml (2.2ml/kg body weight) containing 0.8mg/ml DMT and 0.21 mg/ml harmine, 1 dosing session*	None	None	Mean HAM-D score reduced by 62% on day 1 (p = 0.01), 72% on day 7 (p = 0.001), and 45% on day 14 (p=0.11). Scores significantly decreased at day 21 (% not reported).
Sanches 2016[19] & Zeifman 2021[22] N=17	Mean age: 42.71 % female: NR % non-Hispanic White: NR	HAMD: 19.2 (5.5) NR	Ayahuasca *120–200ml (2.2ml/kg body weight) containing 0.8mg/ml DMT and 0.21 mg/ml harmine, 1 dosing session*	None	None	HAM-D and MADRS score decreased from 80 to 180 minutes after ayahuasca (p < 0.01) and from day 1 to day 21 (p = 0.000). Suicidality decreased at from baseline to 1, 7, 14, and 21 days after administration with the largest effect at 21 days (Hedges' g = 1.75).

Notes. [a] Weighted mean calculated across intervention and control groups; [b] Clinically meaningful response defined as reduction in HAM-D score by at least 50% and remission defined as HAM-D ≤7.
Abbreviations. CI=confidence interval; CSSRS=Columbia Suicide Severity Rating Scale; DMT=5-methoxy-N,N-dimethyltryptamine, a psychedelic of the tryptamine class; GRID-HAMD=GRID-Hamilton Depression Rating Scale; HAM-D=Hamilton Rating Scale for Depression; MADRS-SI=Montgomery-Asberg Depression Rating Scale – Suicidal Ideation; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; SMD=standardized mean difference.

OPIOID USE

Ibogaine may not reduce short-term opioid withdrawal symptoms compared to placebo. Our confidence in this finding is low based on the small number of studies available, study methodologic limitations, and inconsistent findings. Although several pre-post studies[24-28] found that ibogaine use was associated with a reduction in opioid withdrawal symptoms, this finding was not replicated in an RCT (Table 7).[23] Whether ibogaine use is associated with long-term opioid use reduction is unclear. Only 3 small uncontrolled observational studies with high attrition have evaluated long-term outcomes. Available evidence is therefore insufficient to draw conclusions about the long-term efficacy of ibogaine. Importantly, ibogaine has been associated with serious adverse events, namely prolonged QTc interval on an electrocardiogram (ECG) and cardiac arrhythmia. Across studies, 1 death occurred during treatment.

Only 1 small RCT has been conducted on ibogaine use to treat opioid withdrawal symptoms. In this trial[23] (which was conducted in New Zealand and designed to evaluate ibogaine safety), 27 participants on methadone treatment for OUD were randomized to receive 1 of 3 doses of noribogaine (an ibogaine active metabolite at 60mg, 120mg, or 240mg) or placebo in the immediate time period following their last use of an opioid. In the week before receiving noribogaine, participants stopped methadone and received long-acting morphine for 6 days followed by short-acting morphine for 1 day. Approximately 2 hours after their last dose of short-acting morphine, participants received noribogaine or placebo and were monitored for withdrawal symptoms. The study's primary efficacy outcome was the time in hours before participants requested a dose of morphine or methadone. The trial found that noribogaine at any dose did not result in a longer time to resuming opioid use (and did not significantly reduce withdrawal symptoms) compared to placebo, noting that participants in both groups were treated in the same physical space and could have influenced each other. None of the participants experienced serious adverse effects. Norigobaine was associated with dose-dependent effect on QTc interval prolongation on electrocardiogram, which is a risk factor for life-threatening cardiac arrhythmias. The trial did not follow participants long term.

In a small uncontrolled observational study[27] in the Netherlands with similar research aims as the New Zealand trial, 14 adults on methadone treatment for OUD who were transitioned to morphine received ibogaine 10mg/kg and were monitored for withdrawal. Most participants (11/14, 79%) did not restart morphine within 24 hours, and among these participants the median Clinical Opiate Withdrawal Scale (COWS) score was 0, indicating no or mild withdrawal symptoms. Half of participants had a prolonged QTc >500ms during the treatment period (a change from baseline) and received magnesium infusions as a result, without any adverse consequences. All participants experienced ataxia with an inability to walk without support, which reversed within 48 hours. Like the New Zealand trial, this study did not follow participants long term.

Four additional uncontrolled observational studies[24-26,28] of adults receiving ibogaine with the intent of opioid detoxification (N = 14–88) found that participants had lower measures of opioid withdrawal and/or opioid craving post-ibogaine compared to pre-ibogaine use. In a small observational study[26] conducted in New Zealand, 14 adults completed treatment for opioid withdrawal with ibogaine 25–55mg/kg, diazepam 5–30mg, and zopiclone 7.5–15mg. On average, participants reported having fewer withdrawal symptoms 12–24 hours after receiving ibogaine compared to baseline. One participant (not included in the analysis) died during

treatment under circumstances that are not well described. In a report by New Zealand officials, the death was deemed very likely "related to ibogaine ingestion and most probably related to a cardiac arrhythmia." A subset of participants (8/14, 57%) were followed for 12 months. Among these participants, the Addiction Severity Index Lite (ASI-Lite) for drug use was significantly lower at 12 months compared with baseline, and most participants (6/8, 75%) had negative drug screens at 12 months. Only 1 other study reported on long-term opioid use. In a retrospective study of 88 adults who received ibogaine at a treatment center in Mexico with a history of heroin (51%) or prescription opioid use (49%), 30% of participants reported never using opioids again, while 48% said that their opioid use was reduced compared to the period before ibogaine treatment, 17% reported no change, and 6% increased their use.[25]

Table 7. Study Characteristics and Outcomes of Psychedelic Treatment for OUD

Study ***Sample Size*** ***Country*** ***Follow-Up***	**Patient Characteristics**	**Psychedelic** ***Dose***	**Co-intervention(s)**	**Comparator**	**Withdrawal and/or Opioid Use Outcomes**
RCT					
Glue 2016[23] N=27 *New Zealand* *~9 days*	Mean age: 41 % female: 22 % non-Hispanic White: 74	Noribogaine[a] *60mg, 120mg, or 180mg, 1 dosing session*	None	0mg placebo	Mean time to opioid substitution treatment = 8.6 hrs in 60mg group vs 22.5 hrs in 120mg group vs 11.4 hrs in 180mg group vs 13.9 hrs in placebo group
Pre-post Observational Studies					
Brown 2018[24] N=30 *Mexico* *12 months*	Mean age: 29 % female: 17 % non-Hispanic White: 90	Ibogaine *1,540 ± 920mg*	None	NA	MD SOWS at mean time interval of 76.5 hrs = 17.0 points ($p < .001$) ASI for drug use = 0.40 at baseline vs 0.17 at 12 months # participants with opioid-free days in the previous 30 days at 12 months = 8.8
Davis 2017[25] N=88 *Mexico* *3 months-3 years*	Age: 41% 25-34 years old, 39% 35-54 years old % female: 27 %non-Hispanic White: 89	Ibogaine *15 mg/kg ±5, 1 dosing session*	Participation in detoxification program	NA	% participants with reduction in cravings = 50% at 1 week; 35% at 3 or more months Opioid use post-treatment: 30% abstinent, 48% returned to use, 17% no change, 6% use increased
Knuijver 2022[27] N=14 *The Netherlands* *24 hours*	Age (median): 48 % female: 14 % non-Hispanic White: NR	Ibogaine *10 mg/kg, 1 dosing session*	None	NA	Return to morphine use within 24 hrs = 79% Median COWS among 5 not on morphine after 24 hrs = 0

Study ***Sample Size*** ***Country*** ***Follow-Up***	**Patient Characteristics**	**Psychedelic** ***Dose***	**Co-intervention(s)**	**Comparator**	**Withdrawal and/or Opioid Use Outcomes**
Malcolm 2018[28] N=50 *Mexico* *48 hours*	Mean age: 31 % female: 39 % non-Hispanic White: 78	Ibogaine *18–20 mg/kg, 1 dosing session*	Participation in detoxification program	NA	Mean COWS before ibogaine = 8.2 at 48 hrs and 7.64 at 24 hrs vs mean COWS after ibogaine = 5.26 at 24 hrs and 3.30 at 48 hrs Mean SOWS before ibogaine = 20.51 at 48 hrs and 17.09 at 24 hrs vs Mean SOWS after ibogaine = 12.63 at 24 hrs and 10.04 at 48 hrs Mean BSCS before ibogaine = 6.58 at 48 hrs and 5.98 at 24 hrs vs mean BCBS after ibogaine = 2.69 at 24 hrs and 1.92 at 48 hrs
Noller 2018[26] N=14 *New Zealand* *12 months*	Mean age: 38 % female: 50 % non-Hispanic White: 100	Ibogaine *25–55 mg/kg (mean 31.4, SD 7.6), 1 dosing session*	Diazepam 5-30mg and zopiclone 7.5–15mg	NA	Mean SOWS = 25.21 at baseline vs 14.21 at 12-24 hrs (p = 0.015) Mean SOWS = 24 at baseline vs 8.5 at 42-84 hrs (p = 0.070) ASI = 0.32 at baseline vs 0.06 at 12 months (p < 0.01) Negative urine drug screen at 12 months = 6/8, 75%

Notes. [a] An ibogaine active metabolite.
Abbreviations. ASI=Addiction Severity Index; BSCS=Brief Substance Craving Scale; COWS=Clinical Opioid Withdrawal Scale; hrs=hours; OOWS=Objective Opiate Withdrawal Scale; OP-SCL=Opiate-Symptom Checklist; SD=standard deviation; SOWS=Subjective Opioid Withdrawal Scale.

ALCOHOL USE

Psilocybin-assisted psychotherapy may reduce heavy drinking days and average alcohol consumption per day among adults with alcohol use disorder. Although results are consistent and direct, our confidence in these findings is low due to study methodologic limitations and small sample sizes. MDMA-assisted psychotherapy for alcohol use has been less studied and evidence is currently insufficient to draw conclusions.

One RCT[29] has been conducted on psilocybin-assisted psychotherapy for alcohol disorder (Table 8). In this US trial, 95 adults with an average of 14 years of alcohol dependence were randomized to receive 12 psychotherapy sessions with 2 psilocybin dosing sessions or diphenhydramine 50–100mg. At baseline, participants in the psilocybin group consumed a mean (SD) of 7.52 (4.58) standard drinks per day (defined as 14 grams of ethanol) compared to 7.10 (4.05) in the diphenhydramine group. The study did not report whether participants had previous experience with treatment for alcohol dependence. Participants receiving psilocybin experienced a significantly greater reduction in the percent of heavy drinking days and number of drinks per day compared to the diphenhydramine group at 32-week follow-up. Reduction in the percent of drinking days also favored psilocybin, but this finding was nonsignificant, and improvements on all outcomes were observed in both groups. No serious adverse events occurred among participants who received psilocybin.

In a small uncontrolled observational study conducted by the same group as the trial,[30] 10 adults were administered a 14-week psilocybin-assisted psychotherapy program that included 1–2 psilocybin dosing sessions starting in week 4. In the period after dosing (weeks 5–12), the percent of heavy drinking days and any drinking days were decreased compared with baseline and with the period prior to the initial dosing of psilocybin. At the study endpoint of 36 weeks, percent heavy drinking days and any drinking days were trending upward but still below baseline.

MDMA-assisted psychotherapy was evaluated as a treatment for alcohol use disorder in a UK study[31] of 14 adults with mostly moderate to severe alcohol use disorder. Participants were enrolled in an 8-week treatment program consisting of 10 psychotherapy sessions, in 2 of which they received MDMA. At 9 months post-treatment, 9 participants were abstinent from alcohol and 2 had reduced their use to fewer than 14 units of alcohol per week.

Table 8. Study Characteristics and Outcomes of Psychedelic-assisted Psychotherapy for AUD

Study ***Sample Size*** ***Country*** ***Follow-up***	**Patient Characteristics**	**Psychedelic** ***Dose***	**Co-intervention(s)**	**Comparator**	**Outcomes**
RCT					
Bogenschutz 2022[29] N=95 *US* *36 weeks*	Mean age: 46 % female: 44 % non-Hispanic White: 79	Psilocybin *Session 1: 25mg/70kg* *Session 2: 30–40mg/70kg*	12 sessions of psychotherapy using motivational enhancement therapy and cognitive behavioral therapy	Diphenhydramine *Session 1: 50mg* *Session 2: 100mg*	MD % heavy drinking days = 13.86, 95% CI [3.00, 24.72] MD % drinking days at baseline = 13.44, 95% CI [–0.18, 27.05] MD drinks per day = 1.09, 95% CI [0.27, 1.92]
Pre-post Observational Studies					
Bogenschutz 2015[30] N=10 *US* *36 weeks*	Mean age: 40 % female: 40 % non-Hispanic White: 30	Psilocybin 0.3–0.4mg/kg	12 psychotherapy sessions	NA	MD % heavy drinking days weeks 5–12 relative to baseline = 26.0, 95% CI [8.7, 43.2] and relative weeks 1–4 = 18.2, 95% CI [2.8, 33.5] MD % drinking days weeks 5–12 relative to baseline = 27.2, 95% CI [9.0, 45.4] and relative weeks 1–4 = 21.9, 95% CI [5.1, 38.6]
Sessa 2021[31] N=14 *UK* *9 months*	Mean age: 48 % female: 43 %non-Hispanic White: NR	MDMA 125mg initial dose, followed by 62.5mg booster dose	10 psychotherapy sessions	NA	9 participants were abstinent from alcohol and 2 reduced use to <14 units of alcohol per week at 9 months follow-up.

Abbreviations. AUD=alcohol use disorder; CI=confidence interval; MD=mean difference; MDMA=3,4-methylenedioxymethamphetamine; NR=not reported.

TOBACCO USE

Evidence regarding psychedelic-assisted psychotherapy for tobacco use is limited to 1 small uncontrolled observational study of psilocybin use, which is insufficient to make conclusions about efficacy. The average participant in this US study[32,33] ($N = 15$) was aged 51, smoked 19 cigarettes per day for a 31 years, and had 6 previous lifetime quit attempts (see Appendix C in the Supplemental Materials for additional study characteristics). The intervention consisted of intensive cognitive behavioral therapy delivered in 19 in-person sessions, with 3 sessions of psilocybin administration as well as brief daily phone calls for 2 weeks following participants' target quit dates. At 12 months, 10/15 (67%) adults were abstinent from smoking as measured by smoking timeline follow-back assessments and verified by exhaled carbon monoxide and urinary cotinine levels. Among those who participated in longer-term follow-up (range: 16–57 months), 9/12 (60%) were abstinent from smoking by the same measures. No serious adverse events were reported.

In addition to its small sample size, a limitation of this study is the potential for selection bias. Although participants were typical of those seeking medical care for tobacco cessation in terms of tobacco use history and the number of quit attempts, most (10/15, 67%) reported past use of hallucinogens. It is possible that the participants with past hallucinogen use had different expectations regarding the potential of this treatment compared to those without past hallucinogen use.

COCAINE AND CANNABIS USE

Psychedelics, specifically ayahuasca and ibogaine, have also been evaluated in uncontrolled observational studies as treatment for other substance use including cocaine and cannabis. Due to study methodologic limitations, small sample sizes, indirectness, and inconsistency, this evidence is insufficient to draw conclusions about the effects of ayahuasca and ibogaine on use of cocaine and cannabis. See Appendix C in the Supplemental Materials for detailed study characteristics.

One observational study[34] evaluated the use of ayahuasca among participants with mixed forms of substance use. In this Canadian pre-post study[34] of 12 adults participating in a 4-day "Working with Addiction and Stress" retreat that incorporated ayahuasca ceremonies, the proportion of participants who reported using alcohol, tobacco, and cocaine declined. No change was observed for opiate or cannabis use, and no serious adverse events were reported.

Three observational studies[36,37,71] of ibogaine have also been conducted among individuals with cocaine or opioid dependence who self-referred to a treatment program on St. Kitts in the West Indies. The largest and most recent study[37] of this treatment program included 102 adults with opioid dependence and 89 with cocaine dependence who underwent 1 ibogaine dosing session during a 12-day inpatient detoxification program. Self-reported cravings as measured by the Heroin (HCQ-29) and Cocaine (CCQ-45) Craving Questionnaires were lower at the time of discharge compared to before treatment, and remained lower among 37 participants with opioid dependence and 32 with cocaine dependence who completed follow-up at 1 month. No serious adverse events were reported, though orthostatic hypotension occurred in 5% of participants and transient nausea, vomiting, and ataxia were reported as common side effects shortly after ibogaine administration.

In a retrospective study[35] of 75 adults in Brazil who underwent 1–9 ibogaine dosing sessions in conjunction with outpatient psychotherapy, 61% of participants reported abstinence. The duration of reported abstinence was longer for participants who underwent multiple ibogaine dosing sessions compared to 1 dosing session (median 8.4 months compared to median 5.5 months). No serious adverse events were reported.

OTHER CONDITIONS

Psychedelic substances have been investigated as treatment for social anxiety, OCD, and for non-specific mood and anxiety symptoms in a single RCT and 2 uncontrolled observational studies. This evidence is insufficient to draw any conclusions about the effectiveness of psychedelics for these disorders. See Appendix C in the Supplemental Materials for detailed study characteristics.

An RCT[38] of 17 adults with clinical symptoms of social anxiety disorder (SAD) found that Beck Anxiety Inventory scores were not significantly different after a single ayahuasca dosing session compared to 0mg placebo.[38] However, ayahuasca was associated with a significant improvement in self-perception of speech performance as measured by the Self-Statements During Public Speaking Scale. In a pre-post study[39] of 9 adults with OCD in the US who received variable doses of psilocybin for up to 4 total treatments, all participants experienced a decrease in OCD symptoms as measured by the Yale-Brown Obsessive Compulsive Scale (23–100% reduction in YBOCS scores).

Lastly, ibogaine plus 5-MeO-DMT has been used as treatment for US Special Forces Veterans with a range of mood and anxiety symptoms. A retrospective study[40] of 51 Veterans who participated in a psychedelic clinical program in Mexico during which they received 1 dose of ibogaine and 3 doses of 5-MeO-DMT found significant reductions in PTSD symptoms (SMD PTSD Checklist-5 = -3.6, $p < 0.001$), depression (SMD Patient Health Questionnaire-2 = -3.7, $p < 0.001$), anxiety (SMD Generalized Anxiety Disorder 2-Item = -3.1, $p < 0.001$), and suicidal ideation (SMD Depressive Symptom Index Suicidality Subscale = -1.9, $p < 0.001$) 30-days post-treatment.

HARMS

Transient side effects were commonly reported and may occur before, during, or after a psychedelic session (for full list of observed harms see Supplemental Materials Appendix C).

Ibogaine has been associated with serious adverse events, including death in 1 study.[26] Several studies found a dose-dependent effect of ibogaine on QTc interval prolongation on ECG, which is a risk factor for cardiac arrhythmia.[23,27] Other common side effects of ibogaine include headache, nausea, imbalance, and visual impairment.

MDMA may also be associated with cardiac risks. Only 1 study reported a serious adverse event attributed to MDMA, a participant with premature ventricular contractions (PVCs) at baseline experienced an increase in PVCs requiring an overnight hospital stay for observation.[2] Other transient side effects of MDMA include symptoms related to mood (*eg*, anxiety, irritability, restlessness), sleep (*eg*, fatigue, insomnia), sensation (*eg*, dizziness, impaired balance), pain (*eg* headache, muscle tension), and gastrointestinal systems (*eg*, nausea, vomiting, low appetite).

Psilocybin was associated with transient effects on heart rate (*eg*, tachycardia, palpitations) and elevated blood pressure, but these events were not described as serious. Common side effects of psilocybin include anxiety, fear, headache, and nausea. Ayahuasca was not associated with serious adverse events in included studies. Common side effects of ayahuasca include headache, nausea, and vomiting.

DISCUSSION

The aim of this review was to synthesize evidence on the benefits and harms of psychedelics as primary or adjunct treatment for mental health and substance use disorders. Given the prevalence of mental health and substance use disorders with the Veteran population, any novel or emerging treatments with the potential to improve clinical outcomes are of great interest.

MDMA-assisted psychotherapy for PTSD is the most extensively studied intervention involving psychedelics. In a clinical research setting, MDMA paired with intensive psychotherapy co-led by 2 mental health professionals may reduce PTSD symptom severity and lead to clinically meaningful improvement and/or disease remission for some participants in the short term. Although results are fairly consistent and direct, trial sample sizes are small and at risk of prognostic imbalance (a failure of randomization to balance groups on participants' responsiveness to treatment). Common side effects of MDMA include anxiety, restlessness, headache, and nausea but serious adverse events appear to be rare.

Although promising, our confidence in these findings is low. The evidence on MDMA-assisted psychotherapy remains preliminary and several important research questions have yet to be addressed. Among these is whether outcomes vary by patient characteristics, index trauma type, disorder severity, or the number or types of past treatments tried. Available evidence also has unclear applicability to Veteran populations, as most studies did not include Veterans and none have been conducted in a VHA setting. Moreover, the psychotherapy component of studied interventions—typically requiring 30 hours or more of psychotherapy co-led by 2 mental health professionals—is more intensive than typically occurs in clinical practice. Researchers are beginning to study whether treatment protocols can be reproduced at scale,[11] but this evidence is preliminary. Whether this level of treatment is feasible in everyday practice and whether treatment benefits may still be observed with lower intensity psychotherapy are questions for future research.

Other interventions involving psychedelics have been less extensively studied. Psilocybin-assisted psychotherapy for depression may reduce symptom severity and lead to sustained remission at 12 months for a proportion of recipients compared to wait list controls, but these same benefits were not observed (in a separate trial) when psilocybin-assisted psychotherapy was compared with psychotherapy and daily escitalopram. We have low confidence in these findings, which are based on 1 small trial for each comparator. Ayahuasca use for depression may be associated with a reduction in short-term symptoms and suicidality. However, our confidence in these findings is also low due to a smaller number of trials with small sample sizes and some inconsistency in results.

Among treatments evaluated for substance use disorders, psilocybin-assisted psychotherapy for alcohol use disorder may reduce alcohol consumption (heavy drinking days and the number of drinks per day), but we have low confidence is this finding (which is based on results of 1 small trial). MDMA-assisted psychotherapy has also been studied for treatment of alcohol use disorder, but results are limited to 1 small observational study and are insufficient to make conclusions. Similarly, evidence on psilocybin as an adjunct to psychotherapy to reduce tobacco use and ayahuasca as treatment for cocaine, cannabis, and other forms of substance use is limited to 1 or a small number of observational studies and is insufficient to make conclusions.

Ibogaine may not reduce opioid-related withdrawal symptoms or reduce long-term opioid use. We have low confidence in these findings, which are drawn from a small number of studies with small sample sizes, study methodologic limitations, and inconsistent findings. Ibogaine had also been studied as a treatment to reduce cocaine use and to reduce problematic general substance use, but results are limited to a small number of observational studies with mixed populations and evidence is insufficient to draw conclusions. Ibogaine plus 5-MeO-DMT was found to improve a range of mood and anxiety symptoms in a retrospective study of US Special Forces Veterans participating in a treatment program in Mexico. However, this study had a high risk of bias and results have not been replicated in other studies. Given safety concerns associated with ibogaine use, particularly the documented risk of QTc prolongation, cardiac arrhythmias, and death, treatment should only be undertaken in the context of a clinical trial with appropriate safety monitoring.

Finally, most available studies on psychedelics required participants to discontinue their usual mental health medications, most often for a least 2 weeks before the study start. Risk of harms arising from medication discontinuation may have been minimal in the research context (due to presumably close patient contact and oversight), but conceivably could be greater in real-world settings. If the recommendation to discontinue medication becomes accepted practice as psychedelics move through the FDA drug development pathway, the risks of doing so must be taken into consideration when assessing the overall balance of risks and benefits of psychedelic treatments.

LIMITATIONS

Limitations of our review methods include our use of sequential review (rather than dual independent review) for data abstraction and risk of bias assessment. Additionally, both statistical precision and heterogeneity can be poorly estimated in small meta-analyses. We took steps to ameliorate these concerns, including use of corrections to better account for uncertainty in the estimation of heterogeneity, but some caution should be used in interpreting reported meta-analytic confidence intervals and prediction intervals.

The available evidence on psychedelics as primary or adjunct treatment for mental health disorders and substance use also has several limitations. First, psychedelics have been studied in a limited number of populations and settings by a relatively small number of researchers and institutions, which has partly been in response to legal and regulatory restrictions. Despite broad recruitment efforts, it is possible that participants of studies to date are not representative of general adult populations with mental health or substance use disorders. For example, US studies have been predominantly conducted among young, mostly non-Hispanic white populations with moderate to severe disease and access to a clinical research center or treatment program. Whether treatment effects can be replicated in a broader array of populations and treatment settings is unclear. Similarly, little is known about the durability of psychedelic treatment effects, as most studies followed participants for no longer than a year. Whether exposure to psychedelics changes the long-term symptomatology of adults diagnosed with PTSD or depression, for example, is largely unknown.

Second, despite the use of low-dose placebos in some trials (*eg*, use of low-dose placebo MDMA in studies of MDMA-assisted psychotherapy for PTSD), many participants were able to correctly guess whether they were in the intervention or comparison groups (among trials that reported this

information). Participant blinding was likely largely ineffective in studies that used a 0mg placebo, which may have biased observed treatment effects.

Lastly, because research on psychedelics is still in an early phase, whether and how psychedelic treatments could fit into usual care pathways is unclear. Even for areas with some promise, such as MDMA-assisted psychotherapy for PTSD, several clinical questions remain including whether benefits are limited to those with moderate to severe disease, whether adults should try more established treatments before considering psychedelic treatment, and if not, which criteria should be met to recommend psychedelics as primary treatment. Available evidence has also not addressed whether those who improve with psychedelic treatments should start or restart other therapies to maintain benefits long term. Additionally, the extent to which psychotherapy protocols employed in interventions involving psychedelics are consistent with current VA/Department of Defense (DoD) guidelines is also unclear. For example, studies of MDMA-assisted psychotherapy for PTSD used the MAPS standard treatment manual to guide psychotherapy sessions, but it is unclear to what degree the MAPS approach overlaps with currently recommended trauma-focused psychotherapies such as Prolonged Exposure as outlined in the applicable VA/DoD guideline (https://www.healthquality.va.gov/guidelines/mh/ptsd/).

FUTURE RESEARCH

Recommendations for future research on psychedelics as primary or adjunct treatment for mental health and substance use disorders include:

- Inclusion of Veteran populations, particularly those with combat-related trauma, with detailed reporting of treatment histories and disease severity at baseline.
- Inclusion of more diverse populations, particularly with respect to race/ethnicity, socioeconomic status, and rurality, to better understand variability in treatment effectiveness, safety, and acceptability.
- Evaluation of the clinical implications of discontinuing mental health medications prior to undergoing psychedelic treatments and whether the benefits of doing so outweigh potential harms.
- Use of low-dose placebo rather than 0mg placebo to improve the adequacy of blinding, and improved reporting of blinding effectiveness.

Questions to be addressed at the health system level include:

- How could and should interventions involving psychedelics be incorporated into current standard of care and usual care pathways?
- Are psychedelic treatment protocols scalable and reproducible across a broad range of regions and settings?
- What are best practices for implementation of psychedelic treatment programs?
- If implemented, how can access to these resource-intensive treatments be distributed equitably?

A large number of underway studies were identified (see Appendix C in the Supplemental Materials for full details) in a wide range of populations (*eg*, adults with PTSD, mood disorders, and substance use). However, most are feasibility or pilot trials that may not fully address these research gaps.

CONCLUSIONS

Novel approaches to treatment of adults with mental health and substance use disorders are needed given the limitations of existing therapies. MDMA-assisted psychotherapy for PTSD, the most extensively studied intervention to date, may reduce PTSD symptom severity and lead to disease remission in a proportion of cases. Psilocybin-assisted psychotherapy and ayahuasca use for depression and psilocybin for alcohol use disorder may also be effective. However, our confidence in these findings is low, mainly due to the small number of trials available and the small sample sizes of these studies. Treatments that utilize psychedelics are still in an early phase of development and many gaps in the evidence need to be addressed. The most critical gaps include whether treatment effects are durable and consistent across patient characteristics and disease severity, whether the benefits of discontinuing mental health medications to undergo psychedelic treatments outweigh risks, and whether psychedelic treatment protocols are reproducible and scalable in everyday practice, including in VHA settings.

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