Technical Report

Emerging and Adjunct Treatments for Common Mental Health Conditions Affecting Veterans:

A Rapid Evidence Assessment

Psychedelic Interventions

2023

GALLIPOLI
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Technical Report (2023)

Emerging and Adjunct Treatments for Common Mental Health Conditions Affecting Veterans: A Rapid Evidence Assessment – Psychedelic Interventions.

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Keywords

rapid review, emerging treatment, adjunct treatment, posttraumatic stress disorder, anxiety disorders, mood disorders, depressive disorders, substance-related disorders, addictive disorders, trauma- and stressor-related disorders, veterans.

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List of Abbreviations

AE – Adverse Event

BMI – Body Mass Index

BDNF – Brain-Derived Neurotrophic Factor

CBD – Cannabidiol

CBN – Cannabinol

CBT – Cognitive Behavioural Therapy

DCS – D-cycloserine

DDVA – Departments of Defence and Veterans' Affairs (Australian Government)

DVA – Department of Veterans' Affairs (Australian Government)

FDA – Food and Drug Administration (US Government)

GMRF – Gallipoli Medical Research Foundation

GRADE – Grading of Recommendations, Assessment, Development and Evaluation

IV – Intravenous

LSD – Lysergic Acid Diethylamide

MA – Meta-analysis

MAOI – Monoamine Oxidase Inhibitor

MDMA – Methylenedioxymethamphetamine

NHMRC – National Health and Medical Research Council (Australian Government)

PICO – Population, Intervention, Comparison, Outcome

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRISMA-S – Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Search

PROSPERO – International Prospective Register of Systematic Reviews

PTSD – Posttraumatic Stress Disorder

RCT – Randomised Controlled Trial

REA – Rapid Evidence Assessment

RRMG – Rapid Reviews Methods Group

RoB 2 – The revised Cochrane risk-of-bias tool for randomised trials

SGB – Stellate Ganglion Block

SNRIs – Selective Norepinephrine Reuptake Inhibitors

SR – Systematic Review

SSRIs – Selective Serotonin Reuptake Inhibitors

TBS – Theta-Burst Stimulation

TGA – Therapeutic Goods Administration (Department of Health and Aged Care, Australian Government)

THC – Tetrahydrocannabinol

TMS – Transcranial Magnetic Stimulation

Assessments and Outcome Measures: Clinician-Administered and Self-Report

Name	Abbreviation
Alcohol Abstinence Self-Efficacy Scale	AASE
Barrett Impulsiveness Scale	BIS-11
Beck Anxiety Inventory	BAI
Beck Depression Inventory – 1A	BDI-1A
Beck Depression Inventory – Second Edition	BDI-II
Behavioral Inhibition System	BIS
Bodily Symptoms Scale	BSS
Brief Experiential Avoidance Questionnaire	BEAQ
Brief Pain Inventory	BPI
Brief Psychiatric Rating Scale	BPRS
Clinical Global Impressions Improvement Scale	CGI-I
Clinical Global Impressions Severity Scale	CGI-S
Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised	CIWA-Ar
Clinician-Administered Dissociative States Scale	CADSS
Clinician-Administered PTSD Scale for DSM-IV	CAPS
Clinician-Administered PTSD Scale for DSM-5	CAPS-5
Columbia Suicide Severity Rating Scale	C-SSRS
Dissociative Experiences Scale II	DES-II
Drug-Taking Confidence Questionnaire	DTCQ
Electroencephalogram	EEG
Emotional Breakthrough Inventory	EBI
Five Facet Mindfulness Questionnaire	FFMQ
Flourishing Scale	FS
Generalized Anxiety Scale	GAD-7
Global Assessment of Functioning	GAF
GRID-Hamilton Depression Rating Scale	GRID-HAMD
Hamilton Anxiety Rating Scale	HAM-A
Hamilton Depression Rating Scale	HAM-D[1]
Hood's Mysticism Scale	HMS
Impact of Event Scale - Revised	IES-R
Laukes Emotional Intensity Scale	LEIS
Liebowitz Social Anxiety Scale	LSAS
Massachusetts General Hospital Antidepressant Treatment Response Questionnaire	MGH-ATRQ
Mindful Attention Awareness Scale	MAAS
Mini International Neuropsychiatric Interview	MINI
Montgomery-Asberg Depression Rating Scale	MADRS
Near-Death Experiences Scale	NDES
Neuroticism Extroversion-Openness-Personality Inventory – Revised	NEO-PI-R
Patient Health Questionnaire	PHQ
Perceived Stress Scale	PSS
Pittsburgh Sleep Quality Index	PSQI
Positive and Negative Syndrome Scale	PANSS

Name	Abbreviation
Post-Traumatic Growth Inventory	PTGI
Psychotropic-Related Sexual Dysfunction Questionnaire	PRSexDQ
PTSD Checklist – Civilian Version	PCL-C
PTSD Checklist for DSM-5	PCL-5
Quick Inventory of Depressive Symptomatology – Self Report	QIDS-SR-16
Self-Statements during Public Speaking Scale	SSPS
Sheehan Disability Scale	SDS
Snaith Hamilton Anhedonia Pleasure Scale	SHAPS
Structured Clinical Interview for DSM-IV Axis I Disorders	SCID-I
Structured Clinical Interview for DSM-5	SCID-5
Structured Clinical Interview for DSM-5, Clinician Version	SCID-5-CV
Suicidal Ideation Attributes Scale	SIDAS
State-Trait Anxiety Inventory	STAI
State-Trait Anxiety Inventory – State subscale	STAI-S
Timeline Followback	TLFB
Visual Analog Mood Scale	VAMS
Visual Analogue Scale – Anxiety	VAS-A
Visual Analogue Scale – Craving	VAS-C
Visual Analogue Scale – Pain	VAS-P
Warwick-Edinburgh Mental Wellbeing Scale	WEMWBS
Work and Social Adjustment Scale	WSAS
Young Mania Rating Scale	YMRS

Notes. 1. The acronyms Ham-D or HDRS are also used in the literature to refer to the Hamilton Depression Rating Scale.

Glossary of Terms

12-month prevalence

The proportion of a target population who have ever fulfilled diagnostic criteria for a codified health condition (e.g., ICD-10/ICD-11; DSM-IV/DSM-5) at some time in their life; and who have experienced symptoms of the health condition in the last 12 months.

Adjunct intervention

An adjunct intervention is added to a primary intervention. The aim of the adjunct intervention is to reduce symptom severity to a greater extent than the primary intervention is expected to achieve alone. When deciding whether an adjunct intervention is effective, one should compare the effectiveness of the primary intervention to the effectiveness of the combined intervention (i.e., primary plus adjunct intervention). Source: Adapted from Jones et al. (2020, p. 5).

Alternative intervention

Alternative interventions are not accepted as best-practice interventions, usually due to a lack of rigorous scientific evidence. These interventions may be popular, or widely used, but are not recommended by treatment guidelines. This does not mean that alternative interventions do not work; it just means that there is not enough evidence to know if they do work. Source: Adapted from Jones et al. (2020, p. 5).

Ayahuasca

See the glossary entry for "Dimethyltryptamine, DMT".

Cannabidiol (CBD)

Cannabidiol is one of the primary cannabinoids found in various concentrations within the cannabis plant. While it is structurally similar to tetrahydrocannabinol (THC), CBD has a diverse pharmacology, and does not cause intoxication or euphoria. CBD has increasingly been investigated in the literature after initially being overlooked in favour of THC (Russo & Marcu, 2017). While the exact mechanism of action is not fully understood, CBD elicits its pharmacological effects (e.g., antiepileptic, anxiolytic, antipsychotic, anti-inflammatory, and neuroprotective) without significant intrinsic activity on CB1 and CB2 receptors, thereby avoiding adverse psychoactive effects (Bridgeman & Abazia, 2017). While data on the long-term safety of CBD is lacking, a longitudinal study of children receiving CBD oil for epilepsy found the most common adverse effects were somnolence (30%) and diarrhoea (24%; Arnold, 2021).

Cannabinoids

Cannabinoids are compounds found in the cannabis plant (i.e., phytocannabinoids: primarily THC and CBD), or synthetic compounds that can interact with the endogenous or "endo-cannabinoid" system. Cannabinoids are usually taken orally (typically as oil or sublingual spray) or inhaled (i.e., smoked, or vaporised). Smoking of medicinal cannabis is generally not advised due to the associated health risks (see the glossary entry for "Vaped and smoked medicinal cannabis"). The endocannabinoid system plays a complex role in physiology, with widespread activity between the central nervous system and most bodily organs. The endocannabinoid system is usually described in relation to two major cannabinoid receptors (CB1 and CB2): cannabinoid receptor type 1 (CB1) is the most abundant receptor expressed primarily in the central nervous system; and cannabinoid receptor type 2 (CB2) is associated with immune function and limited activity in the central nervous system. Source: Adapted from Grinspoon (2021).

Cannabinol (CBN)

Cannabinol is a non-psychoactive cannabinoid found in trace amounts in cannabis. It is the non-enzymatic oxidation by-product of THC; most frequently detected after prolonged and/or inappropriate cannabis storage, especially at higher temperatures (Russo & Marcu, 2017). None of the studies included in this rapid evidence assessment (REA) examined the effects of CBN in isolation from other cannabis constituents.

Classic hallucinogens

"Classic" hallucinogenic or serotonergic tryptamines include lysergic acid diethylamide (LSD), psilocybin, N,N-dimethyltryptamine (DMT), and ayahuasca (the psychoactive compound in ayahuasca is DMT). These compounds belong to the indolamine subclass of monoamine neurotransmitters, which mimic the endogenous neurotransmitter serotonin, and act mainly through agonist activity on various serotonin (5-HT) receptors. Serotonin receptor activity has a wide range of functions including the maintenance of healthy sleep, mood, and behaviour. While 5-HT-receptor-mediated actions are thought to be primarily responsible for the therapeutic effects of serotonergic tryptamines, this mechanism is not sufficient to explain the drug-induced hallucinations associated with many compounds. The neuro-pharmacological evidence base is still developing. The dose and duration of effect for tryptamine derivatives can vary widely depending on their potency and route of administration. Source: Adapted from Frecska et al. (2016).

Clinical trial phases

There are four phases to clinical trials. "Phase 1 are first-in-human trials. These establish basic safety, usually in healthy volunteers who are paid for their participation. Phase 2 are first-in-patient trials. These establish feasibility of a new intervention in a patient population with a particular diagnosis. Phase 3 are efficacy trials. These are randomized, controlled trials, often in very large numbers of similar patients in numerous centers around the world. Phase 3 trials often cost hundreds of millions of dollars and take many years to complete. It is only phase 3 trials that are used to make licensing decisions, because only phase 3 trials have sufficiently robust designs to inform those decisions. Even after licensing, phase 4 trials investigate treatments further, often picking up rare side effects that phase 3 trials can't detect. Licenses are sometimes withdrawn on the basis of phase 4 trials. Even after this, drug safety monitoring is essentially endless, and drugs may be withdrawn for safety reasons after being on the market for many years" (Rucker & Young, 2021, p. 2).

Controversial intervention

Within the context of this report series, controversial interventions refer to healthcare treatments with access barriers (e.g., legislative, regulatory, ethical and/or social), which affect their use in research and clinical practice. Psychedelics and medicinal cannabis are the most controversial interventions examined by the REA. These compounds have a complicated socio-political history and controlled (illegal) status in most countries. In Australia, most psychedelic compounds are classified as Schedule 9 (prohibited) substances (i.e., use is limited to medical and scientific research and subject to regulatory controls); medicinal cannabis and ketamine are classified as Schedule 8 (controlled) substances (i.e., use in a medically controlled environment).

The resurgence of clinical trials examining psychedelic-assisted psychotherapy for various mental health conditions has demonstrated that some compounds (e.g., MDMA) are relatively safe and efficacious in highly controlled research settings (Sessa et al., 2019). Despite the legal barriers, widespread media coverage of these study findings may encourage individuals to seek out these compounds when accepted or conventional treatments fail. Clinicians have an ethical duty to minimise the potential risk of harm to consumers who are currently using (or interested in exploring) psychedelics, albeit within the current regulatory and legislative context (Pilecki et al., 2021). Harm minimisation strategies include education on safety; and the importance of set (i.e., preparation), setting (i.e., support during administration), and therapeutic follow-up (i.e., integration); to help consumers make informed choices about psychedelic use, avoid adverse events, and increase the probability of beneficial effects (Pilecki et al., 2021).

D-cycloserine (DCS)

D-cycloserine (DCS) is an antibiotic. It is traditionally prescribed at high doses as a second-line treatment for tuberculosis, but has increasingly been studied at lower doses in psychiatric conditions (e.g., PTSD, anxiety disorders, substance use disorders) and neurological conditions (e.g., dementia, autism). DCS acts as a partial agonist at the glycine-binding site of the N-methyl-D-aspartate (NMDA) receptor (in vivo, a partial agonist behaves like an agonist at low doses but has features of antagonists at high doses). The NMDA receptor plays a crucial role in cortical neuroplasticity through its influence on long-term potentiation (LTP): a neuronal mechanism thought to be relevant for learning. DCS is thought to enhance the efficacy of therapies that rely on learning processes (e.g., exposure therapy in PTSD and anxiety disorders; and cue-exposure therapy in

substance-related and addictive disorders) by improving fear extinction learning, and memory consolidation and retrieval.

In DCS studies with patients, drug interactions should be considered. There is evidence from animal studies that antidepressants (e.g., imipramine or citalopram) can offset the facilitating effect of DCS on extinction learning. Additionally, neuroleptics (e.g., olanzapine and clozapine) also seem to impair the effects of DCS, especially in patients with schizophrenia. In animal studies, chronic administration of DCS appears to reduce its efficacy; and a meta-analysis of exposure therapy in humans (Norberg et al., 2008) indicates that DCS efficacy is higher when administered a limited number of times, rather than repeatedly. Finally, animal studies indicate that the DCS mechanism of action may change (or even reverse) under conditions of high stress (due to different concentrations of surrounding neurotransmitters), which may be relevant to its efficacy in the treatment of mental health conditions that are characterised by sleep disturbance or fear (e.g., depression, schizophrenia, and anxiety disorders).

DCS is administered orally. At low doses, it is infrequently associated with mild side effects, including dizziness and fatigue. Other side effects on perception and cognition (including hyper-excitability, depression, anxiety, confusion, and memory loss) are mainly associated with high doses. At high doses, gastrointestinal upset, rash, allergy, fever, and cardiovascular problems (including cardiac arrhythmia) have been reported on rare occasions. Very rare reports of seizures have been associated with blood levels exceeding 35 µg/mL; therefore, most studies exclude participants with a history of seizures as a precautionary measure. Source: Adapted from Schade and Paulus (2015).

Diagnostic and Statistical Manual of Mental Disorders (DSM)

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is published by the American Psychiatric Association (APA). It is an international system for classifying mental health disorders using a common language and standard criteria. It is used by clinicians, researchers, policy makers, drug regulation agencies, pharmaceutical companies, health insurance companies, and the legal system. The DSM evolved from systems for collecting census data, psychiatric hospital statistics, and from a United States Army manual. First published in 1952, each revision of the DSM has added psychiatric diagnoses, and removed those no longer considered to be mental health disorders. Criticisms of the DSM include: concerns about the reliability and validity of many diagnoses; the use of categorical distinctions between mental illness and 'normal' functioning; cultural biases; and the medicalisation of human distress. The DSM-IV was published in 1994. The APA collaborated with the WHO as it developed the ICD-10, increasing the alignment between the two classification systems. The DSM-5 was published in 2013, and the text revision (i.e., DSM-5-TR) was published in March 2022. The DSM-5-TR clarified certain diagnostic criteria, but no conceptual changes were made to the criteria sets. Source: Adapted from APA (2022).

Dimethyltryptamine (DMT) – constituent of ayahuasca

N,N-dimethyltryptamine (DMT) is a psychoactive compound that belongs to a class of drugs known as serotonergic (or hallucinogenic) tryptamines (see the glossary entry for "Classic hallucinogens"). DMT is the hallucinogenic component of the psychoactive beverage ayahuasca, which has traditionally been used in cultural and religious rituals in South America. DMT is also abundant in animal and plant organisms, including human blood and brain fluid. Oral consumption of ayahuasca is the most common route of administration and produces hallucinogenic effects within approximately one hour of ingestion, which can last approximately four hours (Fuentes et al. 2020). These effects include a modified state of consciousness and perception, which is thought to allow users to gain insight into maladaptive behavioural, emotional, or cognitive patterns, as well as to confront repressed memories and/or reveal ego defence mechanisms. Initial side effects may include dizziness, diarrhoea, nausea, and vomiting. These effects are common and are often considered an essential part of a process that is intended to bring a sense of "purge" and relief. The characteristic effects of ayahuasca make it difficult to study in a double-blind, placebo-controlled trial; therefore, the long-term risks and benefits are largely unknown. Source: Adapted from Frecska et al. (2016).

Disruptive intervention

Disruptive healthcare interventions are poorly defined in the literature, there is no specific health sector definition, and the term is frequently misapplied to healthcare innovations that may be better described as incremental or radical (Sounderajah et al., 2021). Within the context of this report series, disruptive interventions refer to healthcare innovations that have the potential to challenge established treatment paradigms in a market segment or patient population, leading to market upheaval (Sounderajah et al., 2021). For example, treatment protocols for psychedelic-assisted psychotherapy typically involve two therapists (i.e., a co-therapy team), and three phases of treatment sessions (i.e., preparatory; dosing; integrative), with dosing sessions lasting up to eight (8) hours. A further relevant example involves massed psychotherapy sessions for the treatment of anxiety disorders or PTSD (e.g., the Bergen 4-day treatment protocol for obsessive compulsive disorder; see Kvale et al., 2020). These types of treatment protocols have the potential to disrupt funding models for individual or group psychotherapy, which typically reimburse an individual practitioner for a series of treatment sessions lasting one (1) to two (2) hours. Disruptive interventions exist along a continuum that pose minor to substantial challenges to established treatment paradigms.

Emerging intervention

An intervention where research on treatment effectiveness has commenced, but is still in its infancy, and there is not enough evidence to support its use. These types of interventions may already be used by people with mental health conditions, and are often reported in the media as offering new hope. However, these media reports are typically based on anecdotal evidence or small preliminary studies. This does not mean that emerging interventions do not work; it just means that there is not enough evidence to know if they do work. Source: Adapted from Jones et al. (2020, p. 5).

Evidence-based intervention

Interventions that have been proven to be effective and are supported by rigorous scientific evidence. They are often recommended by treatment guidelines. Source: Adapted from Jones et al. (2020, p. 5).

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)

A systematic approach for rating the certainty of a body of evidence in systematic reviews and other evidence syntheses (The GRADE Working Group, 2022).

Grey literature

Grey literature refers to a range of different document types (in print and electronic formats) produced across all levels of government, academia, business, and industry that: are protected by intellectual property rights; are of sufficient quality to be collected and preserved by library holdings or institutional repositories; and are not controlled by commercial publishers (Farace & Schopfel, 2010).

International Classification of Diseases (ICD)

The International Classification of Diseases (ICD) is published by the World Health Organisation (WHO). It is the international diagnostic classification standard for reporting morbidity (diseases, injuries, and symptoms), mortality (deaths), reasons for encounter, factors that influence health status, and external causes of disease. It is used by clinicians and researchers around the world to store, retrieve, and analyse health information. Specific uses include sharing and comparing health information from hospitals, regions, settings, and countries to: monitor the incidence and prevalence of diseases; track reimbursement and resource allocation trends; check compliance with safety and quality guidelines; and inform evidence-based decision making. The ICD-10 was published in 1992. It is used by more than 100 countries around the world, and cited in more than 20,000 scientific articles. The ICD-11 was published in 2019. Source: Adapted from WHO (2022).

Ketamine

Ketamine is referred to as a psychedelic or dissociative anaesthetic (Vollenweider, 2001). It is commonly used in surgical procedures by medical practitioners and veterinarians. When used for anaesthetic purposes, ketamine is usually administered via intravenous (IV) infusion or intramuscular (IM) injection. Dissociation, sedation, and patient comfort is achieved via its partial agonism on opiate mu-receptors. Due to its rapid onset, it is particularly

useful in emergency, disaster relief, and military situations. However, transient respiratory depression can result if improperly administered (i.e., excessive rate of delivery or excessive dose). Ketamine's antagonism on N-methyl-D-aspartate (NMDA) and glutamate receptors plays a significant role in controlling symptoms of depression and acute suicidal ideation. In 2019, the US Food and Drug Administration (FDA) approved esketamine (S-enantiomer of ketamine), in conjunction with an oral antidepressant, for treatment-resistant depression in adults. In 2020, the FDA approved esketamine, in conjunction with an oral antidepressant, to treat depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation. The drug is administered as an intranasal spray under the supervision of a healthcare provider. It is contraindicated in patients with schizophrenia due to its potential for exacerbating the underlying condition via short-term emergence phenomena or delirium, which can occur in up to 6-12% of patients, and last for up to 3 hours. Source: Adapted from Rosenbaum et al. (2022).

Lifetime prevalence

The proportion of a target population who have ever fulfilled diagnostic criteria for a codified health condition (e.g., ICD-10/ICD-11; DSM-IV/DSM-5) at some time in their life.

Lysergic acid diethylamide (LSD)

Lysergic acid diethylamide (LSD) is an ergot derivative and "classic" hallucinogen (see the glossary entry for "Classic hallucinogens"), which was first synthesised for treating postpartum haemorrhage. After the accidental discovery of its psychoactive effects, it was marketed for psychological research from the 1950s. It was prohibited in 1967 in the USA due to increased recreational drug use through the early 1960s, and its association with counterculture movements. Oral administration of LSD is most common in scientific research, often as a single, one-off dose. LSD may produce variety of psychological and sensory effects including euphoria, hallucinations, and delusions, as well as distortions in the perception of time, depth, sound, colour, and touch. Due to these psychoactive effects, use in uncontrolled or unsupervised environments may lead to anxiety, dysphoria, confusion, and unpredictable behaviour, or the exacerbation of pre-existing psychotic disorders. Other possible adverse effects include increased blood pressure and heart rate, requiring precautions in patients with cardiovascular disease. Source: Adapted from Fuentes et al. (2020).

Methylenedioxymethamphetamine (MDMA)

3,4-Methylenedioxymethamphetamine (MDMA) belongs to a class of drugs termed "entactogens" (Vollenweider, 2001). MDMA induces a positive mood state, in conjunction with the activation of prefrontolimbic or paralimbic structures, and the deactivation of the amygdala and thalamus (Vollenweider, 2001). While entactogens (i.e., MDMA and related compounds) have a molecular structure that is similar to both stimulant amphetamines and hallucinogenic phenylethylamines (e.g., mescaline), entactogens' psychedelic-like effects are typically not accompanied by hallucinations (Vollenweider, 2001). Compared to LSD (see the glossary entry for "Lysergic acid diethylamide, LSD"), MDMA is shorter-acting and produces a more easily tolerated altered state of consciousness (Sessa et al., 2019). It enhances the user's feelings of empathy and bonding, and has been used as an adjunct to psychotherapy to access and process traumatic memories (Sessa et al., 2019).

MDMA was first synthesised in 1912 as one of a series of chemical compounds used to develop medications for managing abnormal bleeding. In 1953-54, the US Army conducted a brief series of toxicity studies in animals. In the late 1970s, psychiatrists and psychologists reported benefits of MDMA-assisted therapy in individuals and couples. Widespread recreational use followed thereafter, leading to criminalisation of the compound by the US Drug Enforcement Administration (DEA) in 1985. MDMA is notable for its ability to decrease fear responses, and increase empathy and interpersonal trust. For these reasons, it was expected to be especially useful in treating the emotional activation that accompanies access to traumatic memories in the treatment of PTSD. Source: Adapted from Williams (2017).

While recent clinical trials indicate that therapeutic doses of MDMA are generally well tolerated, adverse effects may include anxiety, restlessness, fatigue, jaw clenching, headache, and transient increases in blood pressure (Kisely et al., 2021). The long-term safety outcomes remain unknown.

Narrative synthesis

Narrative synthesis is an approach that relies primarily on the use of words and text to summarise and explain the findings from the studies included in a systematic literature review. The defining characteristic of a narrative synthesis is the textual approach used to 'tell the story' of the findings from the included studies, although it may involve the manipulation of statistical data. Source: Adapted from Popay et al. (2006, p. 5).

Psilocybin

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a psychoactive compound that belongs to a class of drugs known as "classic" serotonergic (or hallucinogenic) tryptamines (see the glossary entry for "Classic hallucinogens"). Psilocybin can be derived from certain species of mushrooms. When orally administered, the body converts psilocybin to psilocin (4-hydroxy-N,N-dimethyltryptamine). Psilocin acts as a 5-HT agonist, primarily on the 5-HT2A receptor, which is thought to account for the psychotropic effects of the drug. Like ayahuasca, psilocybin has been used for centuries in cultural and religious rituals in Indigenous communities. It is also thought to have a similar mechanism of action to ayahuasca; with mystical-type experiences correlating with therapeutic outcomes, and the less acute adverse effects of the compound (e.g., nausea). Pharmacologically, psilocybin is closely related to LSD, but has been more widely studied in recent research for various mental health conditions, including treatment-resistant depression, anxiety, and substance use disorders. Source: Adapted from Araújo et al. (2015) and Johnson et al. (2017).

While recent clinical trials indicate that therapeutic doses of psilocybin are generally well tolerated, adverse effects may include anxiety, headache, and transient increases in blood pressure (Kisely et al., 2021).

Psychedelic-assisted psychotherapy

Professionally supervised use of novel and classic psychedelic medications (including ketamine, MDMA, psilocybin, ayahuasca, and LSD) as part of a structured psychotherapy protocol; typically including drug-free preparatory (pre-dosing) and integrative (post-dosing) therapy sessions, in addition to the psychedelic-assisted (dosing) therapy sessions (Schenberg, 2018).

Rapid evidence assessment (REA)

A rapid evidence assessment (REA), or rapid review, is "a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting various methods to produce evidence for stakeholders in a resource-efficient manner" (Hamel et al., 2021, p. 80).

Standalone intervention

The only intervention that an individual receives. The intervention is aimed at symptom reduction. A standalone intervention should be compared to a best-practice intervention/s to determine whether it is effective or not. Source: Adapted from Jones et al. (2020, p. 5).

Stellate ganglion block (SGB)

The stellate ganglion block (SGB) procedure is an injection of local anaesthetic (e.g., 0.5% bupivacaine) into a nerve bundle called the stellate ganglion. The stellate ganglion is located at the base of the neck in the cervical region of the spine (between vertebrae C6 and C7). The procedure is designed to temporally block the function of the stellate ganglion (i.e., interrupt the cervical sympathetic chain; Rae Olmsted et al., 2019). It is typically conducted under ultrasound or fluoroscopic guidance. Since the 1940s, SGB has been used to treat a wide range of neurological and neurovascular conditions (e.g., epilepsy, migraines, cerebral haemorrhage, embolisms, and thrombosis). The beneficial psychiatric effects associated with SGB treatment (e.g., reduced anxiety and depression; increased sleep quality) were first reported in 1947. The mechanism by which SGB may improve symptoms of mental health conditions is not well understood. Lipov et al. (2009) hypothesised that the stellate ganglion activates brain structures that increase levels of nerve growth factors and norepinephrine in the brain, leading to pathological brain states that underlie disorders such as PTSD and chronic pain. A right-sided SGB is usually performed, as the maintenance of chronic sympathetic responses is typically associated with the right central autonomic network. Although the procedure is invasive, it has an acceptable level of safety. The use of ultrasound or fluoroscopic guidance further decreases the risks of complication or adverse effects. The most

common serious adverse event reported from a 1992 survey of 45,000 SGBs, performed without fluoroscopic or ultrasonographic guidance, was generalised seizures due to inadvertent intravascular injection of the local anaesthetic. Temporary Horner syndrome is a common side effect of SGB that is caused by the disruption of the nerve pathway from the neck and head to the brain. Source: Adapted from Summers and Nevin (2017) and Rae Olmsted et al. (2019).

Horner Syndrome typically presents as a constricted pupil of the eye, a drooping eyelid, and decreased sweating on the affected side of the face (Khan & Bollu, 2022).

Tetrahydrocannabinol (THC)

Delta-9-tetrahydrocannabinol (THC) naturally occurs in variable concentrations within the cannabis plant. It is one of the primary psychoactive components of cannabis (see also the glossary entry for "Cannabidiol, CBD"). THC's mechanism of action is thought to be primarily mediated by CB1 receptors in the human central nervous system. CB1 receptors are thought to be responsible for the acute adverse effects of THC, ranging from dizziness and anxiety to mood disturbances and psychotic symptoms (Bridgeman & Abazia, 2017). For this reason, most clinical trials exclude participants with a personal or family history of psychosis. Evidence for the long-term safety of THC is mostly derived from recreational rather than medicinal use. Within the medical context, a 3-year randomised controlled trial (RCT) for participants with multiple sclerosis found that THC has an acceptable safety profile, with low-to-moderate toxicity, and a low incidence of serious adverse events (Arnold, 2021).

Theta burst stimulation (TBS)

Theta burst stimulation (TBS) refers to a type of transcranial magnetic stimulation (TMS) intervention that applies pulses of varying frequency to replicate the natural theta rhythm occurring in the hippocampus of the brain. TBS treatment sessions typically have a shorter duration of stimulation than standard repetitive TMS (rTMS) sessions (up to 5 minutes vs. up to 45 minutes, respectively), and fewer pulses are delivered overall. There are two commonly used TBS protocols: continuous (cTBS) and intermittent (iTBS). In cTBS, bursts of three (3) pulses at 50 Hz are delivered every second for either 20 seconds (100 bursts) or 40 seconds (200 bursts). In iTBS, bursts of three (3) pulses are delivered for 2 seconds then repeated every 10 seconds (i.e., cycles of 2 seconds of TBS followed by a pause of 8 seconds. Source: Adapted from Klomjai et al. (2015) and Oberman et al. (2011).

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a neuro-stimulation and neuro-modulation technique. It aims to induce electric currents in the brain to inhibit at low frequency (i.e., 1 Hz), or excite at high frequency (i.e., 10 to 20 Hz), the neurons of a specific brain area. The medical device that delivers the stimulation is referred to as a coil. Repetitive TMS (rTMS) pulses (i.e., electromagnetic fields switched on and off at a very high rate) can modulate the neuronal response (or cortical excitability) beyond the duration of stimulation. These brain changes are proposed to lead to behavioural consequences with therapeutic potential. Inconsistencies in the findings from TMS intervention studies for different mental health conditions (e.g., OCD) have been attributed to varying treatment protocols (e.g., TMS frequency and intensity), which target different brain regions (e.g., the dorsolateral prefrontal cortex, DLPFC, the supplementary motor area, SMA, and the orbitofrontal cortex, OFC; Ziblak et al., 2021). In research settings, TMS intervention studies increasingly employ imaging (e.g., functional magnetic resonance imaging, fMRI) to target specific brain regions, which may improve the rigour and reproducibility of non-invasive brain stimulation studies over time (Rossi et al., 2021).

There is some evidence to suggest that the clinical response to TMS interventions may be affected by handedness and lateralisation of brain function (e.g., hemispheric variation in mood regulation; Fitzgerald et al., 2021). Consequently, some studies recruit participants or report findings based on handedness (i.e., right-handed, left-handed, or ambidextrous), as TMS interventions are typically hemisphere-specific, and handedness and hemispheric laterality may influence the treatment response (Fitzgerald et al., 2021).

TMS has been approved by several countries (including Australia, the US, the UK, Canada, and Israel) as an intervention for medication-resistant, treatment-refractory, depression in adults (Rossi et al., 2009). The US Food and Drug Administration (FDA) cleared the first TMS device for the treatment of Major Depressive Disorder

(MDD) in 2008. Since that time, the FDA has cleared various TMS devices for several additional treatment indications including: cortical mapping (in 2009); migraine headache with aura (in 2013); obsessive compulsive disorder (in 2017); a TBS protocol for treatment of medication-resistant MDD (in 2018); and short-term smoking cessation (in 2020; Cohen et al., 2022). In 2019, the FDA denied a *de novo* request for a TMS device for treatment of Alzheimer's disease (Cohen et al., 2022).

Common side effects of TMS include headache, drowsiness, and dizziness (Ziblak et al., 2021). Depending on the frequency and protocol of stimulation used, transient headache, localised pain, and discomfort range from possible to infrequent (Rossi et al., 2009). The most serious potential side effect of TMS is seizure. Since the late 1990s, the rTMS safety guidelines have been iteratively revised, which has greatly reduced the incidence of associated seizures. Recent estimates of seizure incidence are less than 1% (overall), which is comparable to most psychotropic medications (Stultz et al., 2020).

While TMS is non-invasive, reducing the number of stimuli (pulses), and selecting the minimum effective intensity, is desirable to avoid unnecessary discomfort for the patient (Temesi et al., 2014). This can be achieved by determining an individual's motor threshold, which is defined as the minimum amount of stimulation necessary to elicit a motor response (an involuntary muscle contraction also known as a motor evoked potential, MEP) in at least 50% of all attempts (as determined by visual inspection or electromyography). Motor thresholds are usually determined at rest (i.e., resting motor threshold, RMT), but can also be determined during weak voluntary muscular contraction such as holding a fist or ball (i.e., active motor threshold, AMT).

TMS: Period and carryover effects

Effective TMS interventions appear to require multiple weeks of sessions to achieve a sustained treatment effect. For example, the FDA-approved protocol for treatment of depression (Horvath et al., 2010) employs several weeks of high frequency (10 Hz) rTMS sessions to achieve a treatment effect that lasts several months beyond the period of active stimulation. Furthermore, the duration of the treatment effect may vary depending on: the mental health condition/s or symptom/s targeted by the TMS intervention; the frequency and intensity of stimulation; the brain region/s targeted by the treatment; and individual differences in treatment response. For example, after a 6-week course of deep TMS (dTMS) treatment, Carmi and colleagues (2019) found that approximately 45% of participants had reduced OCD symptoms at the one-month follow up. Liu and colleagues (2020) reported a longer treatment effect for a shorter treatment duration in participants with a heroin use disorder (i.e., after a 4-week course of rTMS targeting the DLPFC, craving severity was reduced for up to 60 days).

In contrast, it is unclear whether the effects of a single TMS session persist beyond the stimulation day. Several studies (Di Lazzaro et al., 2005; Huang et al., 2005; Huang et al., 2009) suggest that the maximum duration of the treatment effect for a single TMS session is a matter of hours (as evidenced by facilitation of motor evoked potentials in the brain). Thus, studies included in the REA that employed a crossover design were not penalised on the risk-of-bias assessments (Domain S: "bias arising from period and carryover effects") provided the study used a washout period that was longer than one day. Finally, it is not yet known whether superior treatment effects would be achieved with a bursting-pattern protocol (i.e., TBS) or a single-frequency protocol (i.e., rTMS).

Vaped and smoked medicinal cannabis

In Australia, a medical practitioner can prescribe numerous medicinal cannabis products (including dried flower formulations) via the Special Access Scheme (SAS) and Authorised Prescriber (AP) pathways (Therapeutic Goods Administration, 2022). Typically, these approvals are granted for the treatment of non-cancer pain and anxiety; however, some prescribers have used the same approval pathways for patients suffering from insomnia and PTSD (Arnold et al., 2020).

In respect of vaped cannabis, vaporising dried cannabis flower using an approved medical device differs from vaping using an electronic cigarette (e-cigarette) device. E-cigarette devices may expose patients to unsafe inhalation of constituent aerosolised "e-liquid" ingredients such as vitamin E acetate, which has been conclusively linked to an increased risk of a novel lung disease termed "e-cigarette or vaping product use-associated lung injury" (EVALI; Centers for Disease Control and Prevention, 2020). Currently, there is insufficient evidence to rule out other chemicals in (THC-containing) e-cigarette products as contributing to the development of EVALI (Centers for Disease Control and Prevention, 2020).

In Australia, prescribed medicinal cannabis products must conform to the Therapeutic Goods Administration (TGA) manufacturing standards, which do not permit formulations for e-cigarette delivery (Therapeutic Goods Administration, 2017). While evidence on the long-term effects of dried cannabis flower vaporisation is still emerging, many practitioners are likely to continue to recommend vaporised cannabis for rapid relief of breakthrough (pain) symptoms, with (daily) oral formulations preferred for maintenance of symptom control (Sihota et al., 2021).

In respect of smoked cannabis, several studies reported in the literature (and included in the REA) use smoking as a route of administration (e.g., Kayser et al., 2020; Bonn-Miller et al., 2021). The TGA explicitly recommends against the use of smoked cannabis due to the health risks associated with the inhalation of combusted plant matter (i.e., exposure to harmful compounds such as tar, carbon monoxide, and hydrocarbons; Therapeutic Goods Administration, 2017). In contrast, vaporisation heats the plant matter without igniting it, resulting in a vapour that is relatively free from the by-products of combustion. While this is an important harm-reduction strategy for cannabis smokers, the long-term health effects of dried cannabis vaporisation are unknown as it is a relatively new route of administration (Loflin & Earlywine, 2015). In the context of the REA, studies that use smoked cannabis as a route of administration (i.e., Kayser et al., 2020; Bonn-Miller et al., 2021) have been analysed in keeping with this serious limitation on the intervention's generalisability to the medical context (i.e., these studies have been penalised in the "directness" domain of the GRADE certainty of evidence summaries).

Veteran

A current- or former-serving member of the military having had one or more days of continuous, full-time military service in the Permanent or Reserve Forces (Australian definition). The definition of veteran varies by country. In the UK, the term refers to an individual who has served for at least one day in Her Majesty's Armed Forces (Regular or Reserve), or Merchant Mariners who have served on legally-defined military operations (UK Office for Veterans' Affairs, 2020). In Canada, the term applies to any former member of the Canadian Armed Forces with an honourable discharge, who successfully underwent basic training (Government of Canada, 2019). In the US, the term refers to an individual who has served full-time in the active military, naval, or air service (including service as a cadet at the United States Military, Air Force, or Coast Guard Academy, or as a midshipman at the United States Naval Academy), and who was discharged under conditions other than dishonourable (US Department of Veterans Affairs, 2019). In New Zealand, the term applies to an individual who has served in the New Zealand Armed Forces before 1 April 1974; and after that date, individuals with qualifying operational service (i.e., service at a time of war, or on deployments overseas where a ministerial declaration has confirmed a significant risk of harm; New Zealand Defence Force, 2018).

Executive Summary

Background

There are a number of treatments that have an emerging evidence base and could be considered in the management of common mental health conditions affecting veterans. Emerging and adjunct treatments are typically considered when an individual's adherence or response to accepted or conventional treatment/s is poor (i.e., chronic, treatment-resistant, or treatment-refractory mental health conditions).

Aim

The aim of the rapid evidence assessment (REA) was to identify and critically evaluate the current evidence on emerging and adjunct treatments for posttraumatic stress disorder (PTSD) and common mental health conditions affecting veterans.

Rapid evidence assessment

A REA, or rapid review, is "a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting various methods to produce evidence for stakeholders in a resource-efficient manner" (Hamel et al., 2021, p. 80).

Current evidence

The REA examined the peer-reviewed literature published from 1 January 2017 to 8 February 2022.

Emerging and adjunct treatments

The REA examined five categories of interventions as follows:

1. Psychedelic compounds; specifically:
    a. Ketamine;
    b. Methylenedioxymethamphetamine (MDMA);
    c. Lysergic acid diethylamide (LSD);
    d. Psilocybin;
    e. Dimethyltryptamine (DMT) including ayahuasca.
2. Medicinal cannabis; specifically:
    a. Cannabidiol (CBD);
    b. Cannabinol (CBN);
    c. Tetrahydrocannabinol (THC).
3. D-cycloserine (DCS).
4. Stellate ganglion block (SGB).
5. Transcranial magnetic stimulation (TMS) including theta-burst stimulation (TBS).

Common mental health conditions affecting veterans

The REA examined four categories of mental health conditions as follows:

1. Anxiety disorder/s;
2. Mood or depressive disorder/s;
3. Substance-related and addictive disorder/s;
4. Trauma- and stressor-related disorder/s.

The REA included a specific focus on PTSD. Note that, in 2013, when the DSM-IV was revised to the DSM-5, PTSD was moved from the anxiety disorder/s category to the trauma- and stressor-related disorder/s category.

Search strategy

A comprehensive search strategy was developed in consultation with the review team, the GMRF Expert Panel, the DVA Emerging Treatments Project Team, and a liaison librarian (information specialist) with extensive experience developing search strategies for systematic reviews of health and medical research. In keeping with the best-practice guidelines (Garritty et al., 2020; Rethlefsen et al., 2021), the search strategy was peer-reviewed by a senior liaison librarian with an extensive background in health and medical research.

Four electronic databases (PubMed; APA PsycNet; Cochrane Library; PTSDpubs) were searched to identify peer-reviewed, English-language studies of human adults (18 years of age and over) that were published between 1 January 2017 and 8 February 2022. There was a specific emphasis on Level I and Level II evidence as defined by the National Health and Medical and Research Council (NHMRC, 2009). That is, the REA focused on the following three types of publications:

1. Systematic reviews (SRs);
2. Meta-analyses (MAs);
3. Randomised controlled trials (RCTs).

Results: Psychedelic interventions

From the four (4) databases that were searched, 51 studies met the inclusion criteria; including 35 secondary sources: 21 systematic reviews (SRs) and 14 SRs with accompanying MAs. The studies within these secondary sources (i.e., those contained within SRs and MAs) were extracted to a database containing the primary sources (i.e., randomised controlled trials, RCTs). From this collated set of articles (538 in total), all studies that did not meet the inclusion criteria were excluded (e.g., cohort and case-control studies), and all duplicate studies were removed (i.e., often the same RCT would appear in multiple SRs and MAs, as well as being directly retrieved by the search strategy). The final set of articles included 18 RCTs (see Appendix 5). The findings from these studies were narratively synthesised, and risk of bias assessments were conducted for each RCT. Six (6) articles contained additional analyses of one or more of the 18 RCTs included in the REA. The references to these articles are listed within the summary of findings table for each corresponding RCT (see Appendix 7).

Risk of bias assessments: Psychedelic interventions

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2; Sterne et al., 2019) was used to conduct the risk-of-bias assessments for the REA. The three categories of overall risk-of-bias judgements for the RoB 2 tool are "low risk of bias", "some concerns", and "high risk of bias" (Sterne et al., 2019). Of the 18 RCTs of psychedelic interventions included in the REA, two (2) studies were judged to have a low risk of bias, six (6) studies were judged to have some concerns, and ten (10) studies were judged to have a high risk of bias (see Appendix 8).

GRADE certainty of evidence summaries: Psychedelic interventions

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) is a structured, best-practice approach for assessing the certainty of a body of evidence. The REA used the approach recommended by Murad et al. (2017) for grading narrative summaries of a body of evidence where individual studies measure or report different outcomes. The interpretation of the four levels of evidence used in the GRADE profile are as follows:

GRADE	Definition
High ⊕⊕⊕⊕	High confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect.
Moderate ⊕⊕⊕	Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very Low ⊕	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Source: Adapted from NHMRC (2019).

The GRADE certainty of evidence summaries for the psychedelic interventions are as follows:

Intervention (no. of studies)	Design (no. of studies)	RoB Assessments (no. of studies)	Precision and Consistency	Directness	Publication Bias	GRADE Summary[1,2]
Ketamine (11)	Parallel arm RCT (7) Crossover RCT (4)	Serious (7 high risk; 3 some concerns; 1 low risk)	Serious	Not serious	Not suspected	Low ⨁⨁
MDMA (3)	Parallel arm RCT (3)	Not serious, borderline (0 high risk; 3 some concerns; 0 low risk)	Not serious, borderline	Not serious	Not suspected	Moderate ⨁⨁⨁
Psilocybin (2)	Parallel arm RCT (2)	Not serious, borderline (1 high risk; 0 some concerns; 1 low risk)	Serious	Not serious	Not suspected	Low ⨁
Ayahuasca (2)	Parallel arm RCT (2)	Serious (2 high risk; 0 some concerns; 0 low risk)	Serious	Serious	Not suspected	Very Low ⨁
LSD (0)	X	X	X	X	X	X

Notes. LSD = Lysergic acid diethylamide. MDMA = Methylenedioxymethamphetamine. RCT = randomised controlled trial. 1. GRADE summary includes the risk of bias assessments, precision of the effect estimates, consistency of the individual study results, how directly the evidence answers the question of interest, and risk of publication or reporting biases (NHMRC, 2019). 2. Commonly used symbols to describe the certainty of evidence in evidence profiles: High ⨁⨁⨁⨁, Moderate ⨁⨁⨁, Low ⨁⨁, and Very Low ⨁.

Strengths and limitations

Strengths of the REA include the focus on peer-reviewed Level I and Level II evidence (NHMRC, 2009) from scientific journals in the fields of health, medicine, psychiatry, and psychology (including a specialist database developed by the US Department of Veterans' Affairs focusing on literature relevant to veterans with PTSD). Limitations of the REA include the exclusion of potentially relevant papers that were published prior to 2017 and the exclusion of non-English language papers.

Only four studies contained sample sizes over 60 participants (Abdallah et al., 2022; Daly et al., 2021; Grabski et al., 2020; and Mitchell et al., 2021). Moreover, most studies had relatively short follow-up periods (except for: Dakwar et al., 2020; Grabski et al., 2022; Mithoefer et al., 2018; Ot'alora et al., 2018; and Pradhan et al., 2018). Thus, further methodologically robust research on psychedelic interventions, conducted with larger cohorts over longer follow-up periods, is warranted.

Conclusions and recommendations for future research

Based on the literature reviewed in this report, there is insufficient high-quality evidence to support direct policy and practice recommendations in relation to the use of psychedelic compounds as standalone or combined interventions for common mental health conditions affecting veterans (i.e., anxiety disorders, mood/depressive disorders, substance-related and addictive disorders, and trauma and stressor-related disorders). The one exception may be the FDA-approved use of esketamine nasal spray (in combination with an oral antidepressant) for treatment-resistant Major Depressive Disorder (MDD; US Food & Drug Administration, 2019).

The findings from the REA provide some guidance as to a productive direction for future research efforts. There is an opportunity for researchers and funding bodies to consider further investment in high-quality studies of psychedelic compounds as (standalone or combined) interventions for common mental health conditions. Some studies support the use of psychedelics as viable options in individuals with chronic, treatment-resistant, or treatment-refractory mental health conditions. For example, the use of esketamine (as an adjunct to anti-depressant pharmacotherapy) for individuals with treatment-resistant depression and comorbid anxiety (Daly et al., 2021), or MDMA-assisted psychotherapy for individuals with PTSD and a history of poor tolerance, or poor response, to pharmacotherapy or psychotherapy (Mithoefer et al., 2018). The REA identified twenty (20) clinical trial records for studies examining a psychedelic intervention for common mental health conditions (see Appendix 4 for details). The findings from these studies may be relevant to future reports.

The lack of long-term follow-up for the primary outcomes of interest was a major concern for the ketamine studies. Except for two studies (i.e., Grabski et al., 2022; Pradhan et al., 2017), these studies were conducted over a period of four (4) weeks or less. The short study durations may be due (in part) to the rapid onset of ketamine effects, which diminishes over three (3) to seven (7) days (Daly et al., 2021). These effects may be reinforced by psychotherapy, which was only included in four studies (Dakwar et al., 2020; Dakwar et al., 2019; Grabski et al., 2022; Pradhan et al., 2017), potentially limiting the external validity of the findings.

Clinicians and consumers must be advised that little is known about the safety and utility of psychedelic compounds beyond highly controlled research settings. When psychedelic compounds are used as an adjunct to supportive psychotherapy (in the context of an ongoing therapeutic alliance), they may enhance the therapeutic effect of both interventions. However, supervision by an appropriately trained clinician/s using an appropriate treatment protocol/s is required to manage the safety and quality risks to consumers in relation to the potential short- and long-term side effects of such interventions. Further research, which fully investigates and evaluates safety concerns, may ultimately increase consumer confidence in the use of psychedelics as standalone and combined interventions; and may increase the range of treatment options available for military and veteran populations with chronic, treatment-resistant, or treatment-refractory mental health conditions.

Introduction

Background

There are a number of treatments that have an emerging evidence base and could be considered in the management of common mental health conditions affecting veterans. Emerging and adjunct treatments are typically considered when an individual's adherence or response to accepted or conventional treatment/s is poor (i.e., chronic, treatment-resistant, or treatment-refractory mental health conditions).

Aim

The aim of the rapid evidence assessment (REA) was to identify and critically evaluate the current evidence on emerging and adjunct treatments for posttraumatic stress disorder (PTSD) and common mental health conditions affecting veterans.

Common mental health conditions in veterans

Several sources of evidence were considered when selecting the four categories of mental health conditions that were the focus of the REA. This evidence is synthesised in Maguire (2020). Briefly, the data from the Transition and Wellbeing Research Programme (Department of Veterans' Affairs, 2020) – jointly commissioned by the Departments of Defence and Veterans' Affairs (Australian Government) – found that: alcohol disorders (47.5%), anxiety disorders (46.1%), and affective disorders (39.6%) were the most common classes of lifetime mental health disorders (ICD-10 criteria) in recently-transitioned (2010-2015) veterans; and one in four (24.9%) transitioned veterans met lifetime criteria for a diagnosis of PTSD (Van Hooff et al., 2018).

Chronic, treatment-resistant, or treatment-refractory mental health conditions

There are several reasons why an individual may have a poor treatment outcome (i.e., treatment is ineffective, partially effective, or the individual experiences a relapse or recurrence of the mental health condition/s targeted by the treatment/s). This can include factors that affect an individual's adherence to treatment and/or their response to treatment (e.g., characteristics of the treatment; characteristics of the mental health condition/s; an individual's personal circumstances; or characteristics of the health service environment). For example, factors intrinsic to the treatment/s (e.g., side effects of medications, or unpleasant emotions experienced during therapy) can affect an individual's decision to continue treatment. Similarly, factors extrinsic to the treatment/s (e.g., ongoing trauma exposure; relationship breakdown; financial hardship; stigma) can affect an individual's willingness and capacity to seek or continue treatment, or can influence their treatment progress. Finally, aspects of the health care system itself can create barriers to treatment access or treatment retention (e.g., geographical distance; long waitlists; high caseloads).

In the literature, there are various criteria employed to define treatment response and treatment resistance. The definition of treatment response varies considerably across studies and is often couched in terms of the health condition of interest and the most frequently employed outcome measure/s. For example, in studies of participants with a PTSD diagnosis, a 10-point reduction on the Clinician Administered PTSD Scale for DSM-IV (CAPS) is a commonly used and validated benchmark for "treatment response" (Illingworth et al., 2021). Studies often define treatment resistance as a failure to respond to at least two evidence-based treatments (e.g., pharmacotherapy and/or psychotherapy).

Categories of intervention

Interventions can be classified as: (i) standalone treatments; or (ii) adjunct treatments (Jones et al. 2020). Interventions can also be classified according to the quality or amount of evidence supporting their use; that is: (iii) evidence-based; (iv) alternative; or (v) emerging treatments (Jones et al., 2020). The definitions employed by the Australian Department of Veterans' Affairs (DVA) are provided in Table 1.

Table 1. Definitions employed by DVA to classify interventions.

Type of intervention	Definition
Standalone	The only intervention that the individual receives. The intervention is aimed at symptom reduction. A standalone intervention should be compared to a best-practice intervention/s to determine whether it is effective or not.
Adjunct	An adjunct intervention is added to a primary intervention. The aim of the adjunct intervention is to reduce symptom severity to a greater extent than the primary intervention is expected to achieve alone. The combined intervention (i.e., adjunct plus primary intervention) should be compared to the primary intervention to determine whether an adjunct intervention is effective or not.
Evidence-based	Interventions that have been proven to be effective and are supported by rigorous scientific evidence. They are often recommended by treatment guidelines.
Alternative	Alternative interventions are not accepted as best-practice interventions, usually due to a lack of rigorous scientific evidence. These interventions may be popular, or widely used, but are not recommended by treatment guidelines. This does not mean that alternative interventions do not work; it just means that there is not enough evidence to know if they do work.
Emerging	An intervention where research on treatment effectiveness has commenced, but is still in its infancy, and there is not enough evidence to support its use. These types of interventions may already be used by people with mental health conditions, and are often reported in the media as offering new hope. However, these media reports are typically based on anecdotal evidence or small preliminary studies. This does not mean that emerging interventions do not work; it just means that there is not enough evidence to know if they do work.

Source: Adapted from Jones et al. (2020, p. 5).

Methods

Design

A REA was conducted to identify and critically evaluate the current literature on emerging and adjunct treatments for PTSD, and common mental health conditions affecting veterans. A REA, or rapid review, is "a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting various methods to produce evidence for stakeholders in a resource-efficient manner" (Hamel et al., 2021, p. 80).

National Health and Medical Research Council (NHMRC): Levels of evidence

The most appropriate study design to answer an intervention research question is Level II evidence (NHMRC, 2009). Level I studies are systematic reviews of appropriate Level II studies. Study designs that are progressively less robust are shown at Levels III and IV (see Table 2). Importantly, regardless of the quality of a systematic review (e.g., "exceptional"), an NHMRC "level of evidence" ranking is based on the risk of bias in the design of the studies contained within the review (NHMRC, 2009, p. 5). For example, a systematic review of cohort and case-control studies would be assigned a Level III-2 evidence ranking because the studies contained within the review likely have poorer internal validity and greater susceptibility to bias (NHMRC, 2009).

Table 2. NHMRC "level of evidence" hierarchy for intervention research questions.

Level of Evidence	Intervention Research Question
I	A systematic review of Level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e., alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study • Interrupted time series with a control group
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Source: NHMRC (2009, p. 15, Table 3); for explanatory notes see: NHMRC (2009, p. 16).

Protocol

The REA employed the best-practice guidelines (see Appendix 1) recommended by the Cochrane Rapid Reviews Methods Group (RRMG; Garritty et al., 2020); with reference to the guidelines specified by the Department of Veterans' Affairs (DVA; Varker et al., 2014). The REA protocol was submitted to the National Centre for Health Research (UK) – International prospective register of systematic reviews (PROSPERO; National Institute for Health Research, n.d.) to provide evidence of the methodological rigour of the project, and the independence of the review findings. The REA protocol can be accessed using the following link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022307924.

Conditions being studied

The REA examined four categories of mental health conditions: anxiety disorders, mood/depressive disorders, substance-related and addictive disorders, and trauma- and stressor-related disorders. There was a specific focus on PTSD. The selection of the four disorder categories corresponding to "common mental health conditions affecting veterans" was informed by data from the Mental Health Prevalence Study (Van Hooff et al., 2018) conducted as part of the Transition and Wellbeing Research Programme (Department of Veterans' Affairs, 2020).

PICO framework

The Population, Intervention, Comparator, Outcome (PICO) framework for the REA is presented in Appendix 2.

Databases

The databases for the REA were selected in consultation with a liaison librarian (information specialist) with extensive experience developing search strategies for systematic reviews of health and medical research:

1. PubMed.
2. APA PsycNet (all databases: APA PsycINFO, APA PsycArticles, APA PsycBooks).
3. The Cochrane Library (all databases: Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials, CENTRAL; Cochrane Clinical Answers).
4. PTSDpubs Database (formerly PILOTS) – US Department of Veterans' Affairs.

Search strategy

The search strategy was specified according to the best-practice guidelines (Rethlefsen et al., 2021). A PubMed (open-access database) search strategy was developed for the interventions of interest (see Appendix 3). The search strategy was developed in consultation with a liaison librarian (information specialist); and peer-reviewed by a senior liaison librarian as recommended by the best-practice guidelines (Garritty et al., 2020; Rethlefsen et al., 2021). Both liaison librarians had extensive experience developing search strategies for systematic reviews of health and medical research. The search strings exclude: (i) street names for drugs (e.g., ecstasy) as these terms retrieved a significant amount of irrelevant literature examining illicit drug use and mental health conditions; and all acronyms (except PTSD and rTMS) as the non-specific use of certain acronyms retrieved a significant amount of irrelevant literature during the development of the search strategy.

Types of studies

Inclusion criteria

1. Peer-reviewed, quantitative, or mixed-methods studies examining an intervention of interest.
2. Study inclusion was restricted to systematic reviews (SRs), meta-analyses (MAs), and randomised controlled trials (RCTs).
3. There was no restriction for study inclusion based on a concurrent treatment/s (i.e., a comparator) if the treatment included an intervention/s of interest (i.e., an adjunct treatment).

Exclusion criteria

1. Grey literature and certain publication types (e.g., comments, editorials, and letters).
2. Qualitative studies.
3. Epidemiological studies and observational studies (e.g., cohort and case-control studies).
4. Studies of human participants under 18 years of age.
5. Animal studies.

Search dates and restrictions

1. Publication date: 1 January 2017 to 8 February 2022 (5-year period).
2. Language: English.
3. Full-text available.
4. Supplementary searching was limited to hand searching of systematic reviews (SRs) and meta-analyses (MAs) within the reference lists of extracted articles following full-text screening.

Context

There was no restriction for study inclusion based on location (e.g., country) or setting (e.g., inpatient; outpatient; community).

Risk of bias assessments

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2; Sterne et al., 2019) was employed to conduct the risk-of-bias assessments for the REA. For individually randomised trials, the tool is structured into five domains that are based on theoretical and empirical research (Sterne et al., 2019):

1. Bias arising from the randomisation process (D1);
2. Bias due to deviations from intended interventions (D2);
3. Bias due to missing outcome data (D3);
4. Bias in measurement of the outcome (D4);
5. Bias in selection of the reported result (D5).

The five risk-of-bias domains (D1 – D5) are mandatory; and encompass all types of bias that can affect the results from randomised trials. For crossover designs, an additional risk-of-bias domain (DS) is employed to assess bias arising from period and carryover effects. No additional domains are required to assign an overall risk-of-bias judgment to a given study. The three categories of overall risk-of-bias judgements for the RoB 2 tool are presented in Table 3.

Table 3. Overall risk-of-bias judgements for the revised Cochrane risk-of-bias tool for randomised trials.

Overall risk-of-bias judgement	Criteria
Low risk of bias	The study is judged to be at low risk of bias for all domains.
Some concerns	The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain.
High risk of bias	The study is judged to be at high risk of bias in at least one domain. OR The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Source: Adapted from Sterne et al. (2019, p. 5, Table 3).

GRADE certainty of evidence assessments

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) is a structured, best-practice approach to assessing the certainty of a body of evidence. It is used by international organisations that develop clinical guidelines (e.g., Cochrane; World Health Organization, WHO; UK National Institute for Health and Care Excellence, NICE; and the Australian National Health and Medical Research Council, NHMRC). A GRADE assessment considers five factors that may affect confidence in the synthesised findings of a body of evidence (Guyatt et al., 2011; Murad et al., 2017). The five factors are as follows:

1. Risk of bias;
2. Precision of the effect estimates;
3. Consistency of the individual study results;
4. How directly the evidence answers the research question of interest;
5. Risk of publication or reporting biases.

These five factors are combined to provide an overall GRADE assessment for a body of evidence (see Table 4). The REA used the approach recommended by Murad et al. (2017) for grading narrative summaries of a body of evidence where individual studies measure or report different outcomes.

Table 4. Interpretation of the four levels of evidence used in the GRADE profile.

GRADE	Definition
High ⊕⊕⊕⊕	High confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect.
Moderate ⊕⊕⊕	Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very Low ⊕	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Source: Adapted from NHMRC (2019).

Data extraction (selection and coding)

The study selection and coding process involved the following six phases:

1. The liaison librarian translated the PubMed search strategies for the other three databases; conducted the literature searches; generated the Endnote libraries; de-duplicated the retrieved citations in Endnote; and uploaded the citations to Covidence for screening.

2. A standardised title and abstract form was developed by three reviewers, and trialled by two reviewers, on the same 50 abstracts to calibrate and test the review form. Two reviewers independently screened all titles and abstracts, and a third reviewer resolved any conflicts.
3. A standardised full-text form was developed by three reviewers, and trialled by two reviewers, on the same 10 full-text articles to calibrate and test the review form. One reviewer screened all included full-text articles. Excluded full-text articles were screened by a second reviewer and any conflicts were resolved by a third reviewer.
4. One reviewer extracted data from the studies using a piloted form with a set of required data items (e.g., study characteristics, participant characteristics, main findings, and conclusions). A second reviewer checked the accuracy and completeness of the extracted data.
5. One reviewer performed the risk of bias appraisal. A second reviewer verified all judgements and support statements; a third reviewer resolved any conflicts.
6. One reviewer performed the GRADE certainty of evidence assessments. A second reviewer verified all judgements and support statements; a third reviewer resolved any conflicts.

Data synthesis

The review team synthesised and collated the data; and drafted, reviewed, and edited the draft report. The GMRF Expert Advisory Panel and the DVA Emerging Treatments Project Team reviewed the draft report. The report provides:

1. A PRISMA diagram (Results section).
2. A narrative synthesis of the findings (Summary of the Evidence section).
3. A list of the studies excluded during the full-text screening phase (Appendix 4: List of Excluded Studies).
4. A list of the included studies (Appendix 5: List of Included Studies).
5. A matrix of the included studies broken down by intervention type and disorder category (Appendix 6: Matrix of Included Studies).
6. Evidence summaries of the included studies (Appendix 7: Summary of Findings)
7. Risk of bias assessments (Appendix 8: Risk of Bias Assessments, RoB2).
8. GRADE certainty of evidence summaries (Appendix 9: GRADE Certainty of Evidence Summaries).

Review software

Software was used to facilitate review management and ensure a fully transparent review process. Specifically, EndNote X9/20 (Clarivate, 2022) was used for citation management, Covidence (Veritas Health Innovation, n.d.) was used for title/abstract and full-text screening, and Microsoft Excel 2016 (Microsoft Corporation, 2022) was used for data extraction, the risk of bias assessments (RoB 2), and for grading the certainty of the evidence (GRADE).

Results: Psychedelic Interventions

Figure 1 presents the number of articles that were considered at each stage of the REA (i.e., identification, screening, eligibility, and included). The citations for the full-text articles that were excluded during the eligibility assessment are presented in Appendix 4 (based on the reason for exclusion).

From the four (4) databases that were searched, 51 studies met the inclusion criteria; including 35 secondary sources: 21 systematic reviews (SRs) and 14 SRs with accompanying meta-analyses (MAs). The studies within these secondary sources (i.e., those contained within SRs and MAs) were extracted to a database containing the primary sources (i.e., randomised controlled trials, RCTs). From this collated set of articles (538 in total), all studies that did not meet the inclusion criteria were excluded (e.g., cohort and case-control studies), and all duplicate studies were removed (i.e., often the same RCT would appear in multiple SRs and MAs, as well as being directly retrieved by the search strategy).

The final set of articles included 18 RCTs (see Appendix 5). The findings from these studies were narratively synthesised, and risk-of-bias assessments were conducted for each RCT. Six (6) articles contained additional analyses of at least one (1) of the 18 RCTs included in the REA. References to these articles are listed within the summary of findings table for each corresponding RCT (see Appendix 7).

Psychedelic compounds: Standalone and combined interventions (n = 18)

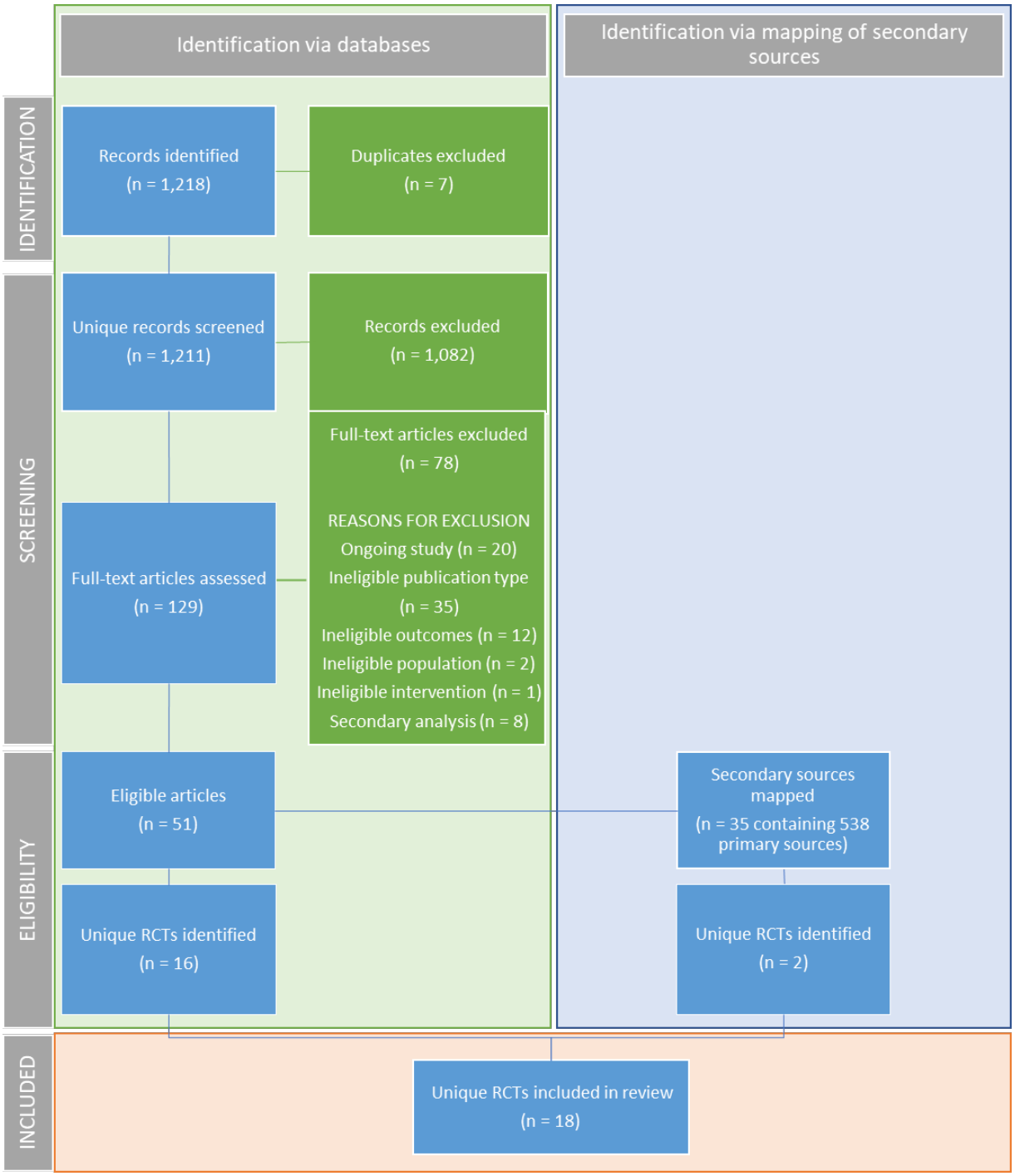

Figure 1. PRISMA diagram detailing the number of records under consideration at each stage of the REA for the psychedelic interventions.

Summary of the Evidence: Psychedelic Interventions

This section of the report summarises the evidence relevant to the use of psychedelic interventions for four categories of mental health conditions: anxiety disorders, mood/depressive disorders, substance-related and addictive disorders, and trauma- and stressor-related disorders.

Eighteen (18) studies of psychedelic interventions met the inclusion criteria for the REA. Eight (8) studies examined standalone interventions, where the study focused on the effect of a psychedelic intervention on the outcome/s of interest (e.g., improvements in mental health symptoms; safety/adverse effects). Ten (10) studies examined combined interventions, where a psychedelic intervention was used in conjunction with a pharmacological intervention (e.g., antidepressant medication) or a psychotherapeutic intervention (i.e., psychedelic-assisted psychotherapy). It is important to note that many of the studies of "standalone" psychedelic interventions did not exclude participants who were stabilised on other pharmacological intervention/s (e.g., antidepressants; anti-psychotics; mood stabilisers) or psychotherapeutic intervention/s (e.g., cognitive behavioural therapy, CBT).

Appendix 6 presents a matrix of standalone and combined psychedelic interventions for the 18 studies, broken down by the disorder categories of interest. Appendix 7 presents a detailed summary of the evidence from each of the 18 studies; including references to six (6) studies reporting additional analyses (i.e., pooled analyses or meta-analyses that included one or more of the 18 studies that met the REA inclusion criteria). The risk-of-bias assessments (Appendix 8) and the GRADE (certainty of evidence) summaries (Appendix 9) provide additional information that is relevant to the evidence summarised in this section of the report.

Ketamine

Anxiety disorders: Standalone interventions

One study (Taylor et al., 2018) examined a standalone ketamine intervention in participants with social anxiety disorder.

Taylor and colleagues (2018; *n* = 18) recruited participants with a social anxiety disorder (DSM-5 criteria) from the community (i.e., via a clinical trials website, outreach to local peer support groups, and word of mouth). Participants were randomised to receive two treatments: one (40-minute) intravenous (IV) infusion of ketamine (0.5mg/kg) and one (40-minute) IV infusion of saline (placebo) in a crossover design (with a 28-day washout period between infusions). That is, all participants received the ketamine and placebo intervention but in a random order (i.e., one group received ketamine then placebo; the other group received placebo then ketamine). Individuals were included in the study if they had: (i) a score greater than (>) 60 on the Liebowitz Social Anxiety Scale (LSAS); (ii) stable doses of SSRIs, SNRIs, and clomipramine for at least 2 months prior to study enrolment; and (iii) a stable regimen of psychiatric medications for at least one month prior to treatment. Participants were required to discontinue prescribed "as needed" anxiety medications for the duration of the study. The outcome measures were the LSAS (primary outcome measure), Visual Analog Scale – Anxiety (VAS-A), State-Trait Anxiety Inventory – State (STAI-S) subscale, Hamilton Depression Rating Scale (HAM-D), and Clinician Administered Dissociative States Scale (CADSS). Assessments were conducted at multiple time points: pre-infusion, post-treatment (3 hours post-infusion), and follow-up (post-infusion: day 1, 2, 3, 5, 7, 10 and 14). Treatment response was defined (relative to baseline) as: (i) greater than (>) 35% reduction in anxiety symptoms on the LSAS (day 14); and (ii) greater than (>) 50% improvement in VAS-A score at any time-point (day 1 – 14). A significantly greater reduction in anxiety symptoms was observed for the ketamine treatment relative to the placebo treatment on the clinician-assessed LSAS (p = 0.01), but not on the self-reported VAS-A (p = 0.95). The proportion of participants who evidenced a treatment response on the LSAS (i.e., > 35% reduction) was significantly higher for the ketamine (n = 6/18; 33.33%) treatment than for the placebo (n = 0/17; 0.00%) treatment (p = 0.025). The proportion of participants who evidenced a treatment response on the VAS-A (i.e., > 50% improvement) was significantly higher for the ketamine (n = 16/18; 88.89%) treatment than for the placebo (n = 9/17; 52.94%) treatment (p = 0.034). This study was judged to have a high risk of bias. Significant carryover effects (as measured by the LSAS on crossover to the second treatment at day 28) were observed for the ketamine-first group relative to the placebo-first group (p = 0.012). The authors proposed that the carryover

effects could be due to a reduction in social anxiety for the ketamine-first group, which may have prompted this group of participants to engage in more social activities.

Anxiety disorders: Combined interventions

One study (Daly et al., 2021) examined a combined esketamine and antidepressant intervention in participants with treatment-resistant major depressive disorder (MDD; DSM-5 criteria) and comorbid anxiety.

Daly and colleagues (2021; *n* = 223) recruited participants with a primary diagnosis of treatment-resistant MDD (DSM-5 criteria) and comorbid anxiety. Treatment-resistant MDD was defined as a history of non-response to at least (≥) one (1) but no more than (≤) five (5) oral antidepressants. This study was a secondary analysis of data from the TRANSFORM-2 randomised controlled trial, but was included in the REA as 72.6% (*n* = 162) of the participants had clinically significant anxiety symptoms or a comorbid anxiety disorder. Specifically, 13.5% (*n* = 30) of participants met criteria for an anxiety disorder on the Mini International Neuropsychiatric Interview (MINI) at screening, and 69.1% (*n* = 154) of participants had a total score of at least (≥) 10 on the Generalized Anxiety Scale (7-item version; GAD-7) at screening and baseline. Participants were required to adhere to their ongoing oral antidepressant for a minimum of two (2) weeks prior to screening, with continued adherence for an additional four (4) weeks during the study screening/observational phase. Following the 4-week screening/observational phase, participants with non-response to their ongoing oral antidepressant, who met the study criteria for treatment-resistant MDD, discontinued all current antidepressant treatment/s. These participants were then randomised to receive a nasal spray (twice per week for four weeks) of either esketamine (randomised flexible dose: 56mg or 84mg) or placebo (saline), in combination with a newly-initiated, open-label, oral antidepressant (daily dose). Outcome measures included the Montgomery-Asberg Depression Rating Scale (MADRS), the GAD-7, and the Clinician Administered Dissociative States Scale (CADSS). Assessments were conducted at multiple time points: baseline, during treatment (day 2, 8, 15, and 22), and post-treatment (day 28). Treatment response was defined (post-treatment relative to baseline) as at least (≥) 50% improvement in depressive symptoms (as measured by the MADRS), and remission was defined as a MADRS score of no more than (≤) 12. At post-treatment, a significantly greater improvement in depressive symptoms (as measured by the MADRS) was observed for participants in the esketamine + antidepressant group compared with those in the placebo + antidepressant group (without comorbid anxiety: $p = .017$; with comorbid anxiety: $p = .036$). The improvement in depressive symptoms did not significantly differ for participants with/without anxiety ($p = .371$). At post-treatment, there was a greater likelihood of meeting criteria for treatment response in the esketamine + antidepressant group compared with the placebo + antidepressant group (with comorbid anxiety: 65.3% vs. 54.2%, respectively; without comorbid anxiety: 79.3% vs. 46.4%, respectively); and a greater likelihood of achieving remission in the esketamine + antidepressant group compared with the placebo + antidepressant group (with comorbid anxiety: 47.2% vs. 33.3%, respectively; without comorbid anxiety: 65.5% vs. 25.0%, respectively). Again, at post-treatment, treatment response ($p = 0.136$) and remission ($p = 0.088$) did not significantly differ for participants with/without anxiety. This study was judged to have a high risk of bias. A higher percentage of participants withdrew from the study due to an adverse event in the esketamine group (7%; *n* = 8/114) compared with the placebo group (0.9%; *n* = 1/109). This difference may be explained by the lack of control for (es)ketamine-specific side effects (e.g., failure to use ondansetron in both study conditions to mask nausea in the intervention condition; see Dadabayev et al., 2020). The lack of control for (es)ketamine-specific side effects also raised concerns about the failure of the study blind (i.e., researchers and participants discerning the allocation to study conditions). Finally, the authors acknowledged several study limitations: (i) at study entry, some participants may no longer have met criteria for an anxiety disorder (i.e., they were being treated with traditional antidepressant therapies and anxiolytic medications); (ii) the analysis did not account for differences in antidepressant dose or concomitant benzodiazepine use; (iii) participants with comorbid anxiety in the placebo + antidepressant group did not have a poorer response to treatment (suggesting that increased contact with site staff may have had a greater effect on these participants); and (iv) preliminary studies have documented higher placebo effects when participants expect to receive a medication with dissociative or hallucinogenic properties.

Mood/depressive disorders

There is an increasing body of evidence demonstrating the rapid and robust antidepressant effects of ketamine for mood/depressive disorders (Corriger & Pickering, 2019; Rosenblat et al., 2019). In early 2019, the US Food

and Drug Administration (FDA) approved esketamine nasal spray (in combination with an oral antidepressant) for treatment-resistant major depressive disorder in adults (US Food & Drug Administration, 2019). This FDA approval was primarily based on results from the TRANSFORM-2 (ClinicalTrials.gov identifier: NCT02418585) and SUSTAIN-1 (ClinicalTrials.gov identifier: NCT02493868) randomised controlled trials. The literature on ketamine interventions for mood or depressive disorders was not reviewed as part of the REA (i.e., this literature was excluded during title/abstract screening to focus on the emerging literature for ketamine interventions).

Substance-related and addictive disorders: Standalone interventions

Two studies examined a standalone ketamine intervention in participants with a cocaine use disorder (Dakwar et. al., 2018; Dakwar et al., 2017).

Both studies recruited participants with a cocaine use disorder (DSM-IV criteria) who were disinterested in treatment or abstinence (i.e., not treatment seeking) from the community (i.e., via referral, advertising, and word of mouth). In both studies, participants were randomised (counterbalanced order) to receive two treatments: one (52-minute) intravenous (IV) infusion of ketamine and one (52-minute) IV infusion of midazolam (active control) in a crossover design (with a 2-week washout period between infusions). That is, all participants received the ketamine and midazolam intervention but in a random order (i.e., one group received ketamine then midazolam; the other group received midazolam then ketamine). In both studies, participants were admitted to hospital (a controlled research unit) up to three times for six (6) days per admission (the infusion was administered on day 4 of each 6-day hospital admission). Each hospital admission was separated by two weeks to control for carryover effects, and to assess cocaine use in the real-world environment (i.e., the "natural ecology"). During the first hospitalisation, all participants received an infusion of normal saline (sham infusion) to identify, and exclude from the research, individuals who did not robustly choose cocaine in the choice task (day 5 of 6-day admission: 70-minute session of five successive choices between 25 mg cocaine or $11). Participants were excluded from the study if they had a dependence on alcohol, benzodiazepines, or opioids, or a personal/family history of psychotic or dissociative symptoms. Assessments were conducted at multiple time points: baseline, post-infusion (day 4 of each 6-day admission), day 5 of each 6-day admission (70-minute choice task), and follow-up (3 times per week for two weeks following each 6-day admission).

In the study by Dakwar and colleagues (2018; n = 18) study, the outcome measures included the Clinician Administered Dissociative States Scale (CADSS), the Hood Mystical Experiences Scale (HMS), and the Near-Death Experiences Scale (NDES), urine toxicology, information on drug use, and medication side effects. In the same group of participants (i.e., crossover design), a significantly greater global improvement (i.e., composite score across three domains: decreases in cocaine craving, cocaine self-administration, and cocaine use in the natural ecology) was observed for the ketamine (56%) treatment compared with the midazolam (20.7%) treatment (p < 0.001). In the study by Dakwar and colleagues (2017; n = 20) study, the outcome measures were not specified: the authors stated they used various assessments and questionnaires pertaining to cocaine craving, reactivity, and medication side effects; and participants provided urine toxicology, and information on drug use. In the same group of participants (i.e., crossover design), a significant reduction in cocaine craving was observed for the ketamine treatment compared with the midazolam treatment prior to discharge (p < 0.01), but not at subsequent time-points (all p's > .05). Additionally, rates of cocaine self-administration were significantly reduced for the ketamine treatment compared with the midazolam treatment at the initial time-point (p < 0.0001), but not at subsequent time-points (all p's > .05). Both studies were judged to have a high risk of bias. The studies employed per-protocol analysis (rather than intention-to-treat analysis) excluding participants due to missing data and protocol deviations following randomisation (Dakwar et al., 2018: 2 participants; Dakwar et al., 2017: 6 participants). Additionally, protocols and pre-specified analysis plans for the studies were not available; therefore, the planned outcome measures and analyses could not be compared with those presented in the published articles.

Substance-related and addictive disorders: Combined interventions

Two studies examined a combined ketamine and psychotherapy intervention in participants with a substance-related disorder: one study recruited participants with a cocaine use disorder (Dakwar et al., 2019); and two studies recruited participants with an alcohol use disorder (Dakwar et al., 2020; Grabski et al., 2020).

Dakwar and colleagues (2019; *n* = 55) recruited treatment-seeking participants with a diagnosis of cocaine dependence (DSM-IV criteria) without additional psychiatric comorbidities from a university-based psychiatric centre. The five-week study had a one-week inpatient phase, and a four-week outpatient phase (two clinic visits per week). Participants were randomised to receive a single (40-minute) intravenous (IV) infusion of either ketamine (0.5 mg/kg; *n* = 27) or midazolam (0.025 mg/kg; *n* = 28) on day 2 of week 1. A blinding procedure was used to minimise expectancy effects: participants were advised they could receive several medications (i.e., amantadine, buspirone, d-cycloserine, ketamine, memantine, midazolam, or saline). All participants received eight (8) sessions of manualised mindfulness-based relapse prevention (MBRP) over a five-week period. Four sessions of MBRP were delivered during the inpatient phase (week 1: day 2 to 5); the remaining four sessions were delivered once per week for four weeks (at one of the two weekly clinic visits; the second weekly visit was with the study physician). The authors' rationale for the initial intensity of the psychotherapy sessions was to provide high-density behavioural treatment during the period (up to 72 hours post-infusion) during which ketamine is hypothesised to exhibit peak psychiatric (and possibly anti-addiction) efficacy to enhance the possibility of sustained behaviour modification. The outcome measures were cocaine-related vulnerabilities such as craving (visual analogue scale), mindfulness (the Five-Facet Mindfulness Questionnaire), stress sensitivity (the Perceived Stress Scale), urine toxicology, and self-reported drug use (cocaine and other substances, including alcohol, benzodiazepines, and ketamine) using the Timeline Followback (TLFB) method. The primary outcomes were end-of-study abstinence and time-to-relapse (defined as first cocaine use or study dropout). Assessments were conducted at multiple time points: twice weekly for 4 weeks (week 2 to 5; outpatient phase), and 6-month follow-up. For end-of-study abstinence, the proportion of participants with urine-test-confirmed abstinence over the last 2 weeks of the study was higher in the ketamine group (48.2%; *n* = 13/27) compared with the midazolam group (10.7%; *n* = 3/28). When route of use (freebase vs. intranasal) was controlled in the analysis, the odds of end-of-study abstinence was 6 times higher in the ketamine group than in the midazolam group ($p = 0.02$). For time-to-relapse, the proportion of participants who used cocaine or dropped out of the study was lower in the ketamine group (57.7%; *n* = 15/27) than the midazolam group (92.9%; *n* = 26/28). When route of use (freebase vs. intranasal) was controlled in the analysis, the ketamine group was 53% less likely to relapse (use cocaine or drop out) compared with the midazolam group ($p = 0.03$). There were no significant between-group differences in alcohol, cannabis, or tobacco use. At the 6-month follow-up (interview conducted via telephone), 44% (*n* = 12/27) of the participants in the ketamine group reported that they were abstinent, compared with none of the participants in the midazolam group; abstinence was significantly associated with treatment group ($p < 0.001$). This study was judged to have a high risk of bias. Several participant baseline characteristics were not reported, which precluded an assessment of the efficacy of randomisation. Additionally, a higher proportion of participants using freebase (as opposed to intranasal) cocaine were in the midazolam group (71%) compared to ketamine group (55%). This may be correlated with the finding that a greater proportion of participants in the midazolam group (57%; *n* = 16/28) discontinued treatment or lost contact compared with the ketamine group (26%; *n* = 7/27). Finally, it is unclear how many participants in the midazolam group could be contacted at the 6-month follow-up (i.e., these numbers were not reported in the published article).

Dakwar and colleagues (2020; *n* = 40) recruited treatment-seeking participants with a diagnosis of alcohol dependence (DSM-IV criteria) without additional psychiatric comorbidities. All participants received six (6) motivational enhancement therapy sessions over a 5-week period. Participants were randomised to receive a single (50-minute) intravenous (IV) infusion of either ketamine (0.6 mg/kg; *n* = 17) or midazolam (0.025 mg/kg; *n* = 23) on a "quit day" during the second week of the study. Participants were included in the study if they met minimum daily/weekly criteria for alcohol use (i.e., at least four heavy drinking days over the past 7 days; or at least 35 drinks/week for men or 28 drinks/week for women). The primary outcomes were daily abstinence (post-infusion: day 1 to 21), time-to-relapse (defined as first heavy drinking day or study dropout), the number of heavy drinking days (day 1 to 21), and urine samples for alcohol use (ethyl glucuronide). Secondary outcome measures included assessments of craving (Visual Analogue Scale – Craving), withdrawal (Clinical Institute Withdrawal Assessment), self-efficacy (Alcohol Abstinence Self-Efficacy Scale and the Drug-Taking Confidence Questionnaire), perceived stress (modified Perceived Stress Scale), mindfulness (Five Facet Mindfulness Questionnaire), and impulsivity (Barrett Impulsiveness Scale). Assessments were conducted at each study visit (2 visits per week for 5 weeks). Post-infusion, days of alcohol abstinence increased in both groups over time (*p*

= 0.004). Ketamine significantly increased the likelihood of abstinence compared with midazolam ($p < 0.001$). This between-group difference was not significant when the analysis was adjusted for total baseline drinks ($p = 0.297$). The time-to-relapse (defined as first heavy drinking day or study dropout) was significantly longer in the ketamine group compared with the midazolam group ($p = 0.04$). However, there were no significant between-group differences in the time to first use, or the time to the first heavy drinking day. The probability of a heavy drinking day increased with each day (post-infusion) for the midazolam group ($p = 0.001$), but not the ketamine group ($p = 0.74$). No significant between-group differences on the secondary outcomes (craving, withdrawal, self-efficacy, mindfulness, stress sensitivity, and impulsivity) were observed for the ketamine group compared with the midazolam group. For the participants who were contactable at the 6-month follow-up (ketamine group: $n = 8$; midazolam group: $n = 11$), abstinence was reported by 75% ($n = 6/8$) of the ketamine group and 27% ($n = 3/11$) of the midazolam group. This study was judged to have a high risk of bias. The authors reported that ketamine significantly increased the likelihood of abstinence, delayed the time to relapse, and reduced the likelihood of heavy drinking days compared with midazolam. However, when the analyses were adjusted to control for baseline levels of drinking, the difference between the ketamine and midazolam group on days of alcohol abstinence was not significant. Statistical analyses of the baseline characteristics were not performed; however, this finding suggests that baseline drinking was higher in the midazolam (comparison) group. Additionally, the time to the first heavy drinking day was not significantly different between groups suggesting that study dropout produced the significant between-group difference in time-to-relapse.

Grabski and colleagues (2020; $n = 96$) recruited participants with a diagnosis of alcohol dependence (DSM-IV/DSM-5 criteria) from the community (via primary and secondary drug and alcohol services, social media, and advertisements). Participants were included in the study if they were currently alcohol abstinent and had a negative urine screen for drugs (excepting cannabis and benzodiazepines). Participants were randomised to one of four conditions (2 x 2 design): three (40-minute) intravenous (IV) infusions (1 to 3 weeks apart) of either ketamine (0.8mg/kg) or saline (0.9%); in combination with either seven (7) sessions of manualised (relapse-prevention-based) psychotherapy or alcohol education (over 8 weeks; the first week was a screening session). The primary outcome measures were days of abstinence (%), and relapse (i.e., one or more days of heavy alcohol use); both measured using the self-report Timeline Followback (TLFB) method. The secondary outcome measures included the Beck Depression Inventory (BDI), the Hamilton Depression Rating Scale (HAM-D), the Short Form Survey (12-item; SF-12), the Psychotomimetic States Inventory, the Fagerström Test for Nicotine Dependence, the Alcohol Craving Questionnaire, and SCRAM bracelet alcohol readings. Assessments were conducted at multiple time points: screening (1 to 28 days before visit 1); baseline (1 to 28 days before visit 1); during treatment (1 to 5 days after visit 2; 4 to 21 days after visit 2; 1 to 5 days after visit 4; 4 to 21 days after visit 4; 1 to 5 days after visit 6; 4 to 21 days after visit 6); and follow-up (11 to 13 weeks after visit 2; 23 to 25 weeks after visit 2). At the 6-month follow-up, a significantly higher number of days abstinent from alcohol was observed for the ketamine group compared with the placebo group across therapy groups ($p \leq 0.05$). The greatest difference in number of days abstinent from alcohol was observed for the ketamine plus psychotherapy group compared with the placebo plus alcohol education group ($p \leq 0.05$). However, no significant differences in relapse rates were observed across the four groups. At the 3-month follow-up, a significant reduction in depressive symptoms (as measured by the BDI) was observed for the ketamine group compared with the placebo group; however, this was not maintained at the 6-month follow-up. No significant differences in depressive symptoms (as measured by HAM-D) at either the 3- or 6-month follow-up were observed across groups. The authors noted that the ketamine treatment was well tolerated, and no serious adverse events were reported. This study was judged to have some risk-of-bias concerns. Almost all participants in the ketamine group, and two-thirds of participants in the placebo group, guessed their allocation to study condition (i.e., failure of the study blind). The authors reported they conducted an intention-to-treat analysis. However, outcome data was missing for 14 of the 96 participants who were lost to follow-up (eight in the ketamine groups and six in the placebo groups).

Trauma- and stressor-related disorders: Standalone interventions

Three studies examined a standalone ketamine intervention in participants with posttraumatic stress disorder (PTSD; Abdallah et al., 2022; Feder et al., 2021; Dadabayev et al., 2020).

Abdallah and colleagues (2022; *n* = 158) recruited veterans and active-duty military personnel with antidepressant-resistant PTSD (DSM-5 criteria) from three military-connected medical centres. Most participants (*n* = 156/158; 99%) met criteria for a major depressive episode (MDE). Antidepressant-resistant PTSD was defined as at least one adequate trial of an FDA-approved antidepressant (for PTSD or depression) as determined by the Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ). Participants were randomised to three (3) conditions and received eight (40-minute) intravenous (IV) infusions (two per week for 4 weeks) of either: (i) standard dose ketamine (0.5 mg/kg; *n* = 51), (ii) low dose ketamine (0.2 mg/kg; *n* = 53), or (iii) placebo (saline; *n* = 54). Participants were included in the study if they were on stable doses of an FDA-approved antidepressant, trazodone, atypical neuroleptic, prazosin, or clonidine for at least 4 weeks prior to randomisation (changes to stable doses were allowed at the investigators' discretion after randomisation); and if they had been engaged in PTSD-focused psychotherapy for 6 weeks prior to randomisation. Outcome measures were the PTSD Checklist for DSM-5 (PCL-5; primary outcome measure), the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinician-Administered Dissociative State Scale (CADSS), and the Positive and Negative Syndrome Scale (PANSS). Assessments were conducted at multiple time points: baseline, during treatment, and follow-up (weekly for 4 weeks after the last infusion). At follow-up, significant improvements in PTSD symptoms (as measured by the PCL-5) were observed over time ($p < 0.0001$); there was no significant effect of treatment group ($p = 0.17$); and the treatment groups did not significantly differ over time ($p = 0.38$). That is, PTSD symptoms improved over time for all groups (i.e., the ketamine groups did not differ from the placebo group on the self-reported primary outcome measure). Similarly, at follow-up, significant improvements in PTSD symptoms (as measured by the CAPS-5) were observed over time ($p < 0.0001$); there was no significant effect of treatment group ($p = 0.46$); and the treatment groups did not significantly differ over time ($p = 0.07$). That is, PTSD symptoms improved over time for all groups (i.e., the ketamine groups did not differ from the placebo group on the clinician-rated secondary outcome measure). This study was judged to have a low risk of bias.

Feder and colleagues (2021; *n* = 30) recruited participants with a diagnosis of chronic PTSD (DSM-5 criteria) from a medical research facility. Participants were randomly assigned to receive six (40-minute) intravenous (IV) infusions (three per week for two consecutive weeks) of either ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg). Individuals were included in the study if they had a score of at least (≥) 30 on the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), and if they had been on stable psychotropic medications (e.g., antidepressants, antipsychotics, or mood stabilisers) for at least 3 months prior to study randomisation. The outcome measures included the CAPS-5, the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impressions Severity (CGI-S) and Improvement (CGI-I) scales, and the Impact of Event Scale – Revised (IES-R). Assessments were conducted at multiple time points: baseline (prior to the first infusion), day 1 (24 hours post-infusion), week 1 (prior to the fourth infusion), and week 2 (after the sixth infusion). Clinical treatment response was defined as at least (≥) 30% reduction on the CAPS-5 (from baseline to week 2). At week 2, a significantly greater improvement in PTSD symptoms (as measured by the CAPS-5) was observed for the ketamine group compared with the midazolam group ($p = 0.0045$): PTSD symptoms were significantly lower in the ketamine group at week 1 ($p = 0.030$), and week 2 ($p = 0.004$), compared with the midazolam group. A significantly greater improvement in depressive symptoms (as measured by the MADRS) was observed for the ketamine group compared with the midazolam group from baseline to week 2 ($p = 0.006$). A significantly greater improvement in global severity (as measured by the CGI-S) was observed for the ketamine group compared with the midazolam group from baseline to week 2 ($p = 0.009$). A significant effect of treatment on global improvement (as measured by the CGI-I) was observed from week 1 to week 2 ($p = 0.004$); it is unclear why the baseline CGI-I data were not included in this analysis. There were no significant differences in symptom improvement from baseline to 24 hours after the first infusion on the total IES-R score ($p = 0.78$), or past 24-hour MADRS score ($p = 0.48$). The likelihood of a treatment response was significantly higher in the ketamine (67%; *n* = 10/15) than in the midazolam (20%; *n* = 3/15) group ($p = 0.03$). Among the ketamine responders, the median time to loss-of-treatment-response was 27.5 days following the 2-week course of infusions. When the integrity of the study blind was evaluated, the percentage of participants who correctly guessed their allocation to study condition did not significantly differ for the ketamine (46.7%; *n* = 7/15) compared with midazolam (35.7%; *n* = 5/14) group throughout the course of the study ($p = 0.55$). Ketamine infusions were well tolerated overall, without serious adverse events. This study was judged to have some risk-of-bias concerns. One participant in the ketamine group dropped out due to lack

of improvement and safety concerns. No pre-specified statistical analysis plan was available. Thus, the planned outcome measures and analyses could not be compared with those reported in the published article.

Dadabayev and colleagues (2020; *n* = 41) recruited participants with chronic pain (minimum duration of 6 months as per the International Association for the Study of Pain, IASP) with or without a comorbid diagnosis of PTSD (DSM-5 criteria), from an outpatient, military-connected, pain clinic. Participants were randomised to receive a single (40-minute) IV infusion of either ketamine (0.5 mg/kg) or ketorolac (15mg; active control). Individuals were included in the study if they were on stable doses of psychotropic and/or pain medications for at least (≥) six weeks prior to study enrolment (and the medication regimen remained stable throughout the study). Additionally, individuals could participate if they were engaged in psychotherapy for PTSD, provided the sessions were stable in duration and frequency and for at least (≥) 6 weeks prior to study enrolment. The outcome measures included the Impact of Event Scale – Revised (IES-R), the Visual Analogue Scale – Pain (VAS-P), and the Brief Pain Inventory (BPI) – Short Form. Assessments were conducted at multiple time points: baseline (pre-infusion), and post-infusion (minute 15, 40, 120, 240; day 1, 2, and 7). The primary end-points were PTSD and CP symptom severity (as measured by the IES-R and VAS-P, respectively) on day 1 and 7 (post-infusion). The analyses of PTSD symptom severity were conducted on the CP + PTSD groups and CP groups separately, as PTSD symptom scores were higher at baseline for the CP + PTSD groups (due to the PTSD diagnosis). In the CP + PTSD groups, PTSD symptom severity (as measured by the IES-R) decreased significantly from baseline to day 7 for both the ketamine and ketorolac treatments ($p < 0.01$); no significant differences were observed for medication type, and no differential effect of medication type was observed from the pre- to post-infusion time points (both *p's* > 0.05). Follow-up analyses revealed significant decreases in PTSD symptoms from baseline to day 1 ($p = 0.03$), and from baseline to day 7 ($p < 0.01$), but not from day 1 to day 7 ($p = 0.37$). In the CP groups, PTSD symptoms did not significantly differ over time (pre- to post-infusion time points), or by medication type (ketamine vs. ketorolac), and there were no differential effects of medication type from the pre- to post-infusion time points (all *p*'s > 0.05). For pain symptoms, there were no significant effects of diagnostic group (CP + PTSD vs. CP) or treatment type (ketamine vs. ketorolac) from baseline to day 1 ($p > 0.10$). There was a significant effect of diagnostic group on pain symptoms over time ($p < 0.01$). While both groups had improved pain scores on day 7; post-hoc analyses revealed that the improvement in pain symptoms was significantly greater in the CP + PTSD group (M = -30.61, SD = 17.71) compared with the CP group (M = -14.28, SD = 15.87) ($p < 0.001$). This study was judged to have some risk-of-bias concerns. There was a significant difference in age ($p = 0.03$) within the CP group between those who received ketamine (younger) and those who received ketorolac (older). The study exclusively used self-report measures, and employed per-protocol analysis (rather than intention-to-treat analysis). No pre-specified statistical analysis plan was available. Thus, the planned outcome measures and analyses could not be compared with those reported in the published article.

Trauma- and stressor-related disorders: Combined interventions

One study examined a combined ketamine and psychotherapy intervention in participants with PTSD (Pradhan et al., 2017).

Pradhan and colleagues (2017; *n* = 10) recruited participants with treatment-refractory PTSD (DSM-IV criteria). Treatment-refractory PTSD was defined as at least 6 months of non-response to treatment-as-usual (i.e., CBT and a therapeutic dose of at least two antidepressants: selective serotonin reuptake inhibitors, SSRIs; and selective norepinephrine reuptake inhibitors, SNRIs). All participants received 12 sessions of individually tailored, mindfulness-based, trauma-focused psychotherapy (i.e., Trauma Interventions using Mindfulness Based Extinction and Reconsolidation for memories, TIMBER): three (3) sessions in week 1 followed by nine (9) sessions conducted on a weekly basis. Participants were randomly assigned to receive a single intravenous (IV) infusion of either ketamine (0.5 mg/kg; *n* = 5) or saline (placebo; *n* = 5). Using a modified crossover design, participants in the placebo group were switched to ketamine after they experienced a sustained relapse of PTSD. The outcome measures included the PTSD Checklist – Civilian Version (PCL-C), Clinician Administered PTSD Scale for DSM-IV (CAPS), the Hamilton Rating Scale for Depression (Ham-D-17), the Beck Anxiety Inventory (BAI), and the Montreal Cognitive Assessment (MoCA). Assessments were conducted at multiple time points: baseline and 8 hours post-infusion. Nine out of the 10 participants (5 of 5 in the ketamine group and 4 of 5 in the placebo group) were identified as treatment responders. Improvements in PTSD symptoms (as measured by CAPS) were observed for both groups ($p < 0.001$). However, no significant between-group differences in PTSD symptoms

(from baseline across all time points) were observed for the ketamine group compared with the placebo group (all *p*'s > .05). A significantly longer duration of treatment response (25 days vs. 49 days) was observed when participants crossed over from the TIMBER-P (placebo) group to the TIMBER-K (ketamine) group ($p = 0.028$). This study was judged to have a high risk of bias. The characteristics of the study groups significantly differed on gender (TIMBER-K: 5 females; TIMBER-P: 3 males, 2 females; $p = 0.038$). The effectiveness of the study blind was not assessed. One participant in the placebo group, who was defined as a non-responder, was excluded from the primary outcome analysis. After crossover, only the outcome (treatment response) with a significant between-group difference was reported. Finally, no pre-specified statistical analysis plan was available. Thus, the planned outcome measures and analyses could not be compared with those reported in the published article.

Methylenedioxymethamphetamine (MDMA)

Anxiety disorders

No included studies examined MDMA for anxiety disorders.

Mood/depressive disorders

No included studies examined MDMA for mood/depressive disorders.

Substance-related and addictive disorders

No included studies examined MDMA for substance-related and addictive disorders.

Trauma- and stressor-related disorders: Combined interventions

Three studies examined a combined MDMA and psychotherapy intervention in participants with PTSD (Mitchell et al., 2021; Mithoefer et al., 2018; Ot'alora et al., 2018).

Mitchell and colleagues (2021; $n = 91$) recruited participants with a diagnosis of severe PTSD (DSM-5 criteria) from the community (via treatment provider referrals, advertisements, and word of mouth). All participants received 15 sessions of manualised supportive therapy with a two-person therapy team: three (90-minute) preparatory sessions; followed by three (3) successive blocks of one (8-hour) psychedelic-assisted therapy session (i.e., MDMA or placebo) and three (90-minute) integrative sessions. There were four (4) weeks between each psychedelic-assisted therapy session and one week between each of the integrative sessions. Participants were randomised to receive either MDMA ($n = 46$) or placebo ($n = 44$) after the second preparatory session (i.e., baseline). Individuals were included in the study if they had a PTSD symptom duration of at least (≥) 6 months on the Mini International Neuropsychiatric Interview (MINI) for DSM-5 at screening, and a CAPS-5 total severity score of at least (≥) 35 at baseline. Prior to the baseline assessments, participants were required to undergo a medically-supervised discontinuation of psychiatric medications for a minimum of five (5) half-lives plus one additional week (where half-life is the time required for the active drug in the body to reduce by half). Across participants, the discontinuation period ranged from 0 days (not required) to 103 days. The outcome measures included the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; primary outcome) and the Sheehan Disability Scale (SDS; secondary outcome). Assessments were conducted at multiple time points: T1 (baseline: second preparatory session); T2 (three weeks after the first psychedelic-assisted session); T3 (three weeks after the second psychedelic-assisted session); T4 (primary endpoint: eight weeks after the third psychedelic-assisted session, which was 18 weeks after baseline). Clinical treatment response was defined as a 10-point decrease on CAPS-5. Loss of diagnosis (specific diagnostic measure on CAPS-5), and remission (loss of diagnosis and total CAPS-5 score of ≤ 11), were measured in both groups. At the primary endpoint (eight weeks after the third psychedelic-assisted session), a significant reduction in PTSD symptoms ($p < 0.0001$), and a significant reduction in functional impairment ($p = 0.0116$), was observed for the MDMA-assisted therapy group compared with the placebo-assisted therapy group. This study was judged to have some risk-of-bias concerns. The authors did not formally assess the efficacy of the study blind; however, at the time of unblinding, participants correctly guessed their allocation to study condition almost 100% of the time.

Mithoefer and colleagues (2018; $n = 26$) recruited military veterans and first responders (firefighters and police officers) with service-related, chronic PTSD (DSM-IV criteria) from the community (via referrals from mental health professionals, internet advertisements, and word of mouth). Participants were randomly assigned (1:1:2) to three dose groups: active-control MDMA (30mg), part-dose MDMA (75mg), or full-dose MDMA (125mg). The

MDMA was administered during two 8-hour manualised psychotherapy sessions (spaced one month apart) with a male or female co-therapy (i.e., two therapist) team (see Mithoefer, 2016). Participants in the active-control (30mg) and part-dose (75mg) MDMA groups subsequently participated in an open-label crossover trial with full dose MDMA (100mg to 125mg). Individuals were included in the study if they had a PTSD symptom duration of at least (≥) 6 months, a total score of at least (≥) 50 on the Clinician Administered PTSD Scale for DSM-IV (CAPS), and non-response (or inability to tolerate) prior pharmacotherapy or psychotherapy. Psychiatric comorbidity was permissible (except bipolar disorder, substance use disorder with remission of 60 days or less, and eating disorders with active purging). Participants were also required to taper and abstain from psychotropic medications during the study except for sedative hypnotics or anxiolytics (used as required) between the MDMA-assisted psychotherapy sessions. The outcome measures included the Clinician Administered PTSD Scale for DSM-IV (CAPS; primary outcome), the Beck Depression Inventory-II (BDI-II), the Pittsburgh Sleep Quality Index (PSQI), the Post-Traumatic Growth Inventory (PTGI), the Neuroticism-Extroversion-Openness-Personality Inventory-Revised (NEO-PI-R), the Dissociative Experiences Scale II (DES-II) and the Global Assessment of Functioning (GAF). Assessments were conducted at multiple time points: baseline and follow-up (1 month and 12 months after the second experimental session). Clinical treatment response was not defined in the study. Significantly greater decreases in PTSD symptoms (as measured by total score on the CAPS) were observed at the primary endpoint (one month after the second MDMA-assisted therapy session) for the full-dose (125mg) MDMA group and part-dose (75mg) MDMA group compared with the active-control (30mg) MDMA group (p = 0.001); no significant differences were found between the 75 mg and 125 mg groups (p = 0.185). In the open-label crossover trial with full-dose (100 to 125 mg) MDMA, PTSD symptoms significantly decreased in the group that had previously received active-control (30 mg) MDMA (p = 0.01). However, no further significant decreases in PTSD symptoms were observed in the group that previously achieved a large treatment response after part-dose (75 mg) MDMA in the blinded segment of the study (p = 0.81). Of the 24 participants who completed the 12-month follow-up, PTSD symptoms (as measured by total score on CAPS) were significantly reduced compared with baseline after all groups received full-dose MDMA (i.e., combined group: p < 0.0001). This study was judged to have some risk-of-bias concerns. Mithoefer and colleagues (2018) acknowledged that the active-control (30mg) MDMA only partially achieved maintenance of the study blind.

Ot'alora and colleagues (2018; n = 28) recruited participants with chronic PTSD (DSM-IV) from the community (via internet advertisements and referrals from mental health professionals). Participants were randomised in a dose-response comparison of two high-dose MDMA conditions (100mg: n = 9; 125mg: n = 13) with low-dose MDMA (40mg: n = 6; active control). The MDMA was administered during two (8-hour) psychotherapy sessions (spaced one month apart) with a male or female co-therapy (i.e., two therapist) team. The high-dose MDMA groups had one additional open-label session; the low-dose group crossed over for three open-label, high-dose sessions. Individuals were included in the study if they had a PTSD symptom duration of at least (≥) 6 months, a total score of at least (≥) 50 on the Clinician Administered PTSD Scale for DSM-IV (CAPS), and non-response to at least one course of pharmacotherapy and/or psychotherapy. The outcome measures were the CAPS (primary outcome), the Beck Depression Inventory-II (BDI-II), Dissociative Experiences Scale-II (DES-II), and the Pittsburgh Sleep Quality Index. Assessments were conducted at multiple time points: (i) baseline; (ii) one month after the second blinded therapy session (primary end-point); (iii) one month after the second open-label, high-dose session; (iv) two months after the third open-label, high-dose session; and (v) 12 months (± one month) after the final high-dose session. Clinical treatment response was defined as at least (≥) 30% decrease in the CAPS total score. In the intention-to-treat set, the high-dose groups had the largest reduction in PTSD symptom severity at the primary endpoint (baseline to one month after the second blinded session); however, the overall treatment effect was not significant (p = 0.52). In the per-protocol set (n = 23), a significant reduction in PTSD symptom severity (as measured by the CAPS) was observed (p = 0.03): a significant reduction in PTSD symptoms was observed for the high-dose 125mg MDMA group (p = 0.01), but not the high-dose 100mg MDMA group (p = 0.10), compared to the low-dose 40mg MDMA group. The per-protocol set included all participants who: (i) completed both blinded sessions; (ii) the primary outcome assessment; and (iii) did not experience a major protocol deviation. At the 12-month follow-up, 76% (n = 19/25) of the participants who completed treatment no longer met criteria for PTSD: for treatment completers, PTSD symptoms (as measured by CAPS) remained significantly lower than at baseline (p < 0.001). This study was judged to have some risk-of-bias concerns, as the active control (low-dose 40mg MDMA) was insufficient to maintain the study blind.

Psilocybin

Anxiety disorders

No included studies examined psilocybin for anxiety disorders.

Mood/depressive disorders: Combined interventions

Two studies examined a combined psilocybin and psychotherapy intervention in participants with a mood/depressive disorder (Davis et al., 2021; Carhart-Harris et al., 2021).

Davis and colleagues (2021; *n* = 27) recruited participants with long-standing, moderate-to-severe, major depressive disorder (MDD; DSM-5 criteria) from the community (via flyers, print advertisements, internet forums, social media, and the study website). Participants were randomised to an immediate-treatment group (*n* = 15), or a delayed-treatment group (8-week waitlist control; *n* = 12). The treatment was two day-long (approximately 11 hours) psilocybin sessions (oral capsules; day 1 dose: 20mg/70 kg; day 2 dose: 30mg/70 kg) in combination with supportive psychotherapy. The study was conducted over an 8-week period and involved at least 18 in-person visits, including the two day-long psilocybin sessions. Individuals were included in the study if they were not currently undergoing pharmacotherapy for depression, and were willing and able to refrain from using antidepressants for at least five (5) half-lives before screening (where half-life is the time required for the active drug in the body to reduce by half), and for up to 4 months following enrolment (until the primary outcome assessment). The primary outcome measure was the GRID-Hamilton Depression Rating Scale (GRID-HAMD; an improved version of the Hamilton Depression Rating Scale). The secondary outcome measures were the Beck Depression Inventory – Second Edition (BDI-II), the Patient Health Questionnaire (PHQ), the Columbia Suicide Severity Rating Scale (C-SSRS), the Hamilton Anxiety Rating Scale (HAM-A), and the State-Trait Anxiety Inventory (STAI). Clinical treatment response was defined as at least (≥) 50% reduction in scores on the GRID-HAMD, and remission was defined as a score of no more than (≤) 7 on the GRID-HAMD. Assessments were conducted at multiple time points. The GRID-HAMD was completed at baseline, week 5, and week 8 for participants in the delayed-treatment group, and at the week 1 and week 4 follow-up visits after the second psilocybin session for participants in both the immediate- and delayed-treatment groups. The secondary outcome measures were completed at each visit. Of the randomised participants, 89% (*n* = 24/27) completed the intervention, and the post-session assessments (week 1 and week 4). A significant reduction in depressive symptoms (as measured by the GRID-HAMD) was observed for the immediate-treatment group (at week 1 and 4) compared with the delayed-treatment group (at comparable time points: week 5 and 8; $p < 0.05$). A rapid decrease in depression symptoms (as measured by the QIDS-SR) was observed from baseline to day 1 ($p < .001$); and remained significant through the week 4 follow-up ($p < .001$). In the overall sample, 17 participants (71%) at week 1, and 17 participants (71%) at week 4, had a clinically significant response to treatment, and 14 participants (58%) at week 1, and 13 participants (54%) at week 4 were in remission. This study was judged to have a high risk of bias. Participants in the delayed-treatment group (8-week waitlist control) group were monitored via weekly telephone calls or in-person visits to assess depressive symptoms and suicide risk. Although this was a safety precaution required by the study protocol, issues with study blind were not addressed in the analysis. Participants were likely aware of the treatment allocations, which may have influenced their responses to the self-reported outcome measures. Additionally, the study employed per-protocol analysis (rather than intention-to treat analysis), excluding three (3) participants following randomisation (two from the immediate-treatment group and one from the delayed-treatment group).

Carhart-Harris and colleagues (2021; *n* = 59) recruited participants with long-standing, moderate-to-severe, Major Depressive Disorder (MDD; criteria not specified) from the community (via clinical trial networks and social media). Participants were randomised to receive either: (i) two doses of psilocybin (25mg) three (3) weeks apart plus six (6) weeks of daily placebo (psilocybin group; *n* = 30); or (ii) two doses of psilocybin (1mg) three (3) weeks apart plus six (6) weeks of daily oral escitalopram (escitalopram group; *n* = 29). All participants received psychological support. Individuals were included in the study if they had a score of at least (≥) 17 on the Hamilton Depression Rating Scale (HAM-D). The primary outcome measure was the Quick Inventory of Depressive Symptomatology–Self-Report (16-item; QIDS-SR-16). Secondary outcome measures were extensive and included the Beck Depression Inventory – 1A (BDI-1A), Hamilton Depression Rating Scale (HAM-D), and Montgomery-Asberg Depression Rating Scale (MADRS). Clinical treatment response was defined as greater than

(>) 50% reduction on the QIDS-SR-16, and remission was defined as a score of no more than (≤) 5 on the QIDS-SR-16. Assessments were conducted at two time points: baseline (7 to 10 days before visit 1) and follow-up (visit 6: 3 weeks after visit 5). At follow-up, no significant differences in depressive symptoms (as measured by the QIDS-SR-16) were observed for psilocybin group compared with the escitalopram group (p = 0.17) in the context of supportive psychotherapy. The percentage of participants who evidenced a treatment response on the QIDS-SR was higher for the psilocybin (70%) group than the escitalopram (48%) group; and the percentage of participants who met criteria for remission on the QIDS-SR was higher for the psilocybin group (57%) than for the escitalopram group (28%). However, there were no significant differences between the psilocybin group and the escitalopram group in terms of treatment response or remission. Whilst secondary outcomes favoured the psilocybin group, the authors acknowledged that no conclusions could be drawn from these data as the between-group analyses were not adjusted for multiple comparisons. This study was judged to have a low risk of bias.

Substance-related and addictive disorders

No included studies examined psilocybin for substance-related and addictive disorders.

Trauma- and stressor-related disorders

No included studies examined psilocybin for trauma- and stressor-related disorders.

Dimethyltryptamine (DMT) as an active constituent of ayahuasca

Anxiety disorders: Standalone intervention

One study investigated a standalone ayahuasca intervention in participants with an anxiety disorder (Dos Santos et al., 2021).

Dos Santos and colleagues (2021; n = 17) recruited volunteer undergraduate students with a diagnosis of social anxiety disorder (DSM-5 criteria) from a university site (randomly selected by three of the study authors from an undergraduate university cohort). Participants were randomised to receive either a single dose of ayahuasca (n = 9) or placebo (n = 8). Individuals were included in the study they had a score of at least (≥) 19 on the Social Phobia Inventory (SPIN; as a cut-off for Social Anxiety Disorder, SAD); or sub-clinical anxiety symptoms of excessive fear, anxiety, or avoidance in social situations (self-report). SAD diagnosis was confirmed using the Structured Clinical Interview for DSM-5 – Clinician Version (SCID-5-CV). Individuals were included in the study if they had no prior use of ayahuasca (self-report), and two (or less) lifetime uses (self-report) of other hallucinogens (LSD, psilocybin, DMT, mescaline, other tryptamines, and phenethylamine). Assessments were conducted at multiple time-points: baseline, during the experimental session, and follow-up (day 7, 14, and 21). The outcome measures were the Self-Statements during Public Speaking Scale (SSPS; 5 time-points: 300 to 355 minutes), the Visual Analog Mood Scale (VAMS; 11 time-points, baseline to 355 minutes), the Bodily Symptoms Scale (BSS; 11 time points, baseline to 355 minutes), and the Beck Anxiety Inventory (BAI: baseline, 240 minutes, and follow-up: day 7, 14, and 21). Clinical treatment response was not defined in the study. A significant between-group difference in self-perception of speech performance (as measured by the SSPS) was observed for the ayahuasca group compared with the placebo group over the time-points relevant to the public speaking test (p = 0.017). There were no significant between-group differences in self-reported anxiety symptoms (as measured by the BAI) over time (p > 0.05). The authors postulated that the lack of effect may be due to the inadequate sample size. This study was judged to have a high risk of bias. A prominent study limitation was that the study blind failed (i.e., both the participants and researchers correctly guessed the allocation to study conditions 100% of the time). Additionally, three participants were excluded from all analyses (except the BAI) due to equipment failure (two in ayahuasca group; one in the placebo group). Finally, while all 17 participants were included in the analysis of the BAI data; the ayahuasca and placebo groups were not comparable at baseline.

Mood/depressive disorders: Standalone intervention

One study investigated a standalone ayahuasca intervention in participants with a mood/depressive disorder (Palhano-Fontes et al., 2019).

Palhano-Fontes and colleagues (2019; n = 29) recruited participants with treatment-resistant depression (DSM-IV criteria) from the community (via referrals from local psychiatric outpatient clinics and media

advertisements). Treatment-resistant depression was defined as an inadequate response to at least two classes of antidepressant medication. Individuals were included in the study if they had moderate-to-severe depressive symptoms at screening (defined as a score of at least 17 on the Hamilton Depression Rating Scale, HAM-D). Participants were randomised to receive either a single dose of ayahuasca (n = 14) or placebo (n = 15). After screening, participants underwent a washout period of two weeks (on average) adjusted to the half-life of their antidepressant medication (where half-life is the time required for the active drug in the body to reduce by half). During dosing, participants had not taken any antidepressant medication for seven (7) days, with only benzodiazepines permitted during the study. The dosing sessions lasted approximately eight (8) hours. Throughout the dosing session, participants received support from at least two investigators, who remained in a separate room and assisted as required. The outcome measures were the HAM-D (primary outcome measure) and the Montgomery-Asberg Depression Rating Scale (MADRS). Assessments were conducted at multiple time-points: baseline (one day before dosing), and post-treatment (after dosing: day 1, 2, and 7). The HAM-D was only administered at baseline and day 7. Clinical treatment response was defined as a reduction of at least (≥) 50% in HAM-D or MADRS scores (relative to baseline), and remission was defined as a score of no more than (≤) 7 on the HAM-D, or no more than (≤) 10 on the MADRS. At day 7, a significant reduction in depressive symptoms (as measured by the HAM-D) was observed for the ayahuasca group compared with the placebo group (p = 0.019). Similarly, depressive symptoms (as measured by the MADRS) were significantly lower in the ayahuasca group compared with the placebo group at day 1 (p = 0.04), day 2 (p = 0.04), and day 7 (p < 0.0001). At day 7, the rate of treatment response (as measured by the HAM-D) was significantly different between groups; with 57% of responders in the ayahuasca group and 20% in the placebo group (p = 0.04). Similarly, the response rate (as measured by the MADRS) was statistically different at day 7; with 64% of responders in the ayahuasca group and 27% in the placebo group (p = 0.04). At day 7, the rate of remission (as measured by the HAM-D) did not significantly differ between groups; with 43% of remitters in the ayahuasca group compared with 13% in the placebo group (p = 0.07). Similarly, at day 7, the remission rate (as measured by the MADRS) was 36% in the ayahuasca group and 7% in the placebo group (p = 0.054). No serious adverse events were observed during or after ayahuasca dosing. This study was judged to have a high risk of bias. The study employed per-protocol analysis (rather than intention-to-treat analysis), excluding six (6) participants following randomisation. There was a potential imbalance in baseline characteristics between groups: participants in the placebo group were older and had lower HAM-D and MADRS scores than those in ayahuasca group. Additionally, no pre-specified statistical analysis plan was available. Thus, the planned outcome measures and analyses could not be compared with those reported in the published article.

Substance-related and addictive Disorders

No included studies examined dimethyltryptamine (DMT) or ayahuasca for substance-related and addictive disorders.

Trauma- and stressor-related disorders

No included studies examined dimethyltryptamine (DMT) or ayahuasca for trauma- and stressor-related disorders.

Lysergic Acid Diethylamide (LSD)

No studies examined Lysergic Acid Diethylamide (LSD) for anxiety disorders, mood/depressive disorders, substance-related or addictive disorders, or trauma- and stressor-related disorders.

Strengths and Limitations

Strengths of the REA include the focus on peer-reviewed Level I and Level II evidence (NHMRC, 2009) from scientific journals in the fields of health, medicine, psychiatry, and psychology (including a specialist database developed by the US Department of Veterans' Affairs focusing on literature relevant to veterans with PTSD). Limitations of the REA include the exclusion of potentially relevant papers that were published prior to 2017 and the exclusion of non-English language papers.

Only four studies had sample sizes over 60 participants (Abdallah et al., 2022; Daly et al., 2021; Grabski et al., 2020; and Mitchell et al., 2021). Moreover, most studies had relatively short follow-up periods (except for: Dakwar et al., 2020; Grabski et al., 2022; Mithoefer et al., 2018; Ot'alora et al., 2018; and Pradhan et al., 2017).

Thus, further methodologically robust research on psychedelic interventions, conducted with larger cohorts over longer follow-up periods, is warranted.

Conclusions and Recommendations for Future Research

Based on the literature reviewed in this report, there is insufficient high-quality evidence to support direct policy and practice recommendations in relation to the use of psychedelic compounds as standalone or combined interventions for common mental health conditions affecting veterans (i.e., anxiety disorders, mood/depressive disorders, substance-related and addictive disorders, and trauma and stressor-related disorders). The one exception may be the FDA-approved use of esketamine nasal spray (in combination with an oral antidepressant) for treatment-resistant Major Depressive Disorder (MDD; US Food & Drug Administration, 2019).

The findings from the REA provide some guidance as to a productive direction for future research efforts. There is an opportunity for researchers and funding bodies to consider further investment in high-quality studies of psychedelic compounds as (standalone or combined) interventions for common mental health conditions. Some studies support the use of psychedelics as viable options in individuals with chronic, treatment-resistant, or treatment-refractory mental health conditions. For example, the use of esketamine (as an adjunct to anti-depressant pharmacotherapy) for individuals with treatment-resistant depression and comorbid anxiety (Daly et al., 2021), or MDMA-assisted psychotherapy for individuals with PTSD and a history of poor tolerance, or poor response, to pharmacotherapy or psychotherapy (Mithoefer et al., 2018).

The lack of long-term follow-up for the primary outcomes of interest was a major concern for the ketamine studies. Except for two studies (i.e., Grabski et al., 2022; Pradhan et al., 2017), these studies were conducted over a period of four (4) weeks or less. The short study durations may be due (in part) to the rapid onset of ketamine effects, which diminishes over three (3) to seven (7) days (Daly et al., 2021). These effects may be reinforced by psychotherapy, which was only included in four studies (Dakwar et al., 2020; Dakwar et al., 2019; Grabski et al., 2022; Pradhan et. al., 2017), potentially limiting the external validity of the findings.

Clinicians and consumers must be advised that little is known about the safety and utility of psychedelic compounds beyond highly controlled research settings. When psychedelic compounds are used as an adjunct to supportive psychotherapy (in the context of an ongoing therapeutic alliance), they may enhance the therapeutic effect of both interventions. However, supervision by an appropriately trained clinician/s using an appropriate treatment protocol/s is required to manage the safety and quality risks to consumers in relation to the potential short- and long-term side effects of such interventions. Further research, which fully investigates and evaluates safety concerns, may ultimately increase consumer confidence in the use of psychedelics as standalone and combined interventions; and may increase the range of treatment options available for military and veteran populations with chronic, treatment-resistant, or treatment-refractory mental health conditions.

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Appendix 1: Best-Practice Guidelines for Rapid Reviews

Cochrane Rapid Reviews Methods Group (RRMG) Recommendations (Garritty et al., 2021)
Setting the research question – topic refinement
• Involve key stakeholders (e.g., review users such as consumers, health professionals, policymakers, decision-makers) to set and refine the review question, eligibility criteria, and the outcomes of interest. Consult with stakeholders throughout the process to ensure the research question is fit for purpose, and regarding any ad-hoc changes that may occur as the review progresses. (R1) • Develop a protocol that includes review questions, PICOS, and inclusion and exclusion criteria.
Setting eligibility criteria
Together with key stakeholders: • Clearly define the population, intervention, comparator, and outcomes. o Limit the number of interventions (R2) and comparators (R3). o Limit the number of outcomes, with a focus on those most important for decision-making. (R4) • Consider date restrictions with a clinical or methodological justification. (R5) • Setting restrictions are appropriate with justification provided. (R6) • Limit the publication language to English; add other languages only if justified. (R7) • Systematic reviews (SRs)[1] should be considered a relevant study design for inclusion. (R8) • Place emphasis on higher quality study designs (e.g., SRs or RCTs); consider a stepwise approach to study design inclusion. (R9)
Searching
• Involve an information specialist. • Limit main database searching to CENTRAL, MEDLINE (e.g., via PubMed), and Embase (if available access). (R10) • Searching of specialized databases (e.g., PsycINFO and CINAHL) is recommended for certain topics but should be restricted to 1–2 additional sources or omitted if time and resources are limited. (R11) • Consider peer review of at least one search strategy (e.g., MEDLINE). (R12) • Limit grey literature and supplemental searching (R13). If justified, search study registries and scan the reference lists of other SRs or included studies after screening of the abstracts and full texts.
Study selection
• Title and abstract screening o Using a standardized title and abstract form, conduct a pilot exercise using the same 30-50 abstracts for the entire screening team to calibrate and test the review form. o Use two reviewers for dual screen of at least 20% (ideally more) of abstracts, with conflict resolution. o Use one reviewer to screen the remaining abstracts and a second reviewer to screen all excluded abstracts, and if needed resolve conflicts. (R14) • Full-text screening o Using a standardized full-text form, conduct a pilot exercise using the same 5-10 full-text articles for the entire screening team to calibrate, and test the review form. o Use one reviewer to screen all included full-text articles and a second reviewer to screen all excluded full-text articles. (R15)
Data extraction
• Use a single reviewer to extract data using a piloted form. Use a second reviewer to check for correctness and completeness of extracted data. (R16) • Limit data extraction to a minimal set of required data items. (R17) • Consider using data from existing SRs to reduce time spent on data extraction. (R18)
Risk of bias assessment
• Use a valid risk of bias tool, if available for the included study designs. • Use a single reviewer to rate risk of bias, with full verification of all judgments (and support statements) by a second reviewer. (R19)

Cochrane Rapid Reviews Methods Group (RRMG) Recommendations (Garritty et al., 2021)
• Limit risk of bias ratings to the most important outcomes, with a focus on those most important for decision-making. (R20)
Synthesis
• Synthesize evidence narratively. • Consider a meta-analysis only if appropriate (i.e., studies are similar enough to pool). (R21) Standards for conducting a meta-analysis for an SR equally apply to an RR. • Use a single reviewer to grade the certainty of evidence, with verification of all judgments (and footnoted rationales) by a second reviewer. (R22)
Other considerations for Cochrane RRs
• RRs should be preceded by a protocol submitted to and approved by Cochrane (R23). • The protocol should be published (e.g., PROSPERO or Open Science Framework) (R24). • Allow for post hoc changes to the protocol (eligibility criteria etc.) as part of an efficient and iterative process (R25). • Document all post hoc changes; and incorporate use of online SR software (e.g., Covidence, DistillerSR, and EPPI-Reviewer) to streamline the process (R26).

Source: Garritty et al. (2021, p. 17; Table 1). Notes: 1. To be considered a systematic review (SR) for screening purposes, studies need to: clearly report inclusion/exclusion criteria; search at least two databases; conduct a risk of bias assessment; and provide a list and synthesis of included studies.

Appendix 2: Population, Intervention, Comparator, Outcome (PICO) Framework

Review Question	What is the current evidence for emerging treatments for Posttraumatic Stress Disorder (PTSD) and common mental health conditions affecting veterans, including adjunct treatments?
Population (P)	INCLUSION CRITERIA: (i) Human studies. (ii) Adults (18 years of age and over). (iii) Diagnosed with: anxiety disorder/s; mood or depressive disorder/s; substance-related and addictive disorder/s; or trauma- and stressor-related disorder/s. (iv) Majority of the intervention sample has been diagnosed using the following classification systems: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), or Fifth Edition (DSM-5); or the International Classification of Diseases, 10th Revision (ICD-10), or 11th Revision (ICD-11). EXCLUSION CRITERIA: (i) Studies of human participants under 18 years of age. (ii) Animal studies.
Intervention/s (I)	1. Stellate ganglion block (SGB). 2. Psychedelic-assisted therapies; specifically: (i) ketamine; (ii) methylenedioxymethamphetamine (MDMA); (iii) lysergic acid diethylamide (LSD); (iv) psilocybin; (v) dimethyltryptamine (DMT). 3. Medicinal cannabis; specifically: (i) cannabidiol (CBD); (ii) cannabinol (CBN); (iii) tetrahydrocannabinol (THC). 4. D-cycloserine (DCS). 5. Repeated transcranial magnetic stimulation (rTMS); including theta-burst stimulation (TBS).
Comparator/s (C)	Interventions considered to be the most effective in treating the mental health condition/s of interest; including those listed as having Level I and Level II evidence (National Health and Medical Research Council, Australian Government) in extant clinical guidelines (e.g., the Australian Psychological Society, 2018).
Outcome/s (O)	MAIN OUTCOMES: (i) Symptom severity using a standardised clinician-rated or self-report instrument for the mental health condition/s of interest including generalisation/maintenance of gains/outcomes (i.e., pre-treatment/during/post-treatment and follow-up measures; as available). (ii) Global Assessment of Functioning (GAF). (iii) Quality of Life (QoL) or Health-Related Quality of Life (HR-QoL). ADDITIONAL OUTCOMES: (i) Rates of response (i.e., non-response or partial-response) to intervention/s. (ii) Rates of remission (i.e., partial or full remission) of mental health condition/s. (iii) Rates of relapse (i.e., return of symptoms) or recurrence (i.e., new episode) of mental health condition/s. (iv) Serious adverse events. (v) Retention/dropout rates. (vi) Cost-effectiveness of intervention/s (as available).

Appendix 3: Search Strategy (PubMed)

Search string: Psychedelic intervention

("Ketamine"[Mesh] OR "N-Methyl-3,4-methylenedioxyamphetamine"[Mesh] OR "Lysergic Acid Diethylamide"[Mesh] OR "Psilocybin"[Mesh] OR "N,N-Dimethyltryptamine"[Mesh] OR "psychedelic assisted psychotherapy"[tiab] OR "psychedelic assisted therapy"[tiab] OR "drug assisted psychotherapy"[tiab] OR "drug assisted therapy"[tiab] OR "ketamine"[tiab] OR "esketamine"[tiab] OR "arketamine"[tiab] OR "methylenedioxymethamphetamine"[tiab] OR "lysergic acid diethylamide"[tiab] OR "psilocybin"[tiab] OR "ayahuasca"[tiab] OR "dimethyltryptamine"[tiab]**)**

Search string: Common mental health conditions affecting veterans

AND ("Trauma and Stressor Related Disorders"[Mesh] OR "Anxiety Disorders"[Mesh] OR "Mood Disorders"[Mesh] OR "Substance-Related Disorders"[Mesh] OR "Behavior, Addictive"[Mesh] OR "trauma and stress related disorders"[tiab] OR "trauma and stress related disorder"[tiab] OR "traumatic stress disorder"[tiab] OR "traumatic stress disorders"[tiab] OR "post traumatic stress"[tiab] OR "posttraumatic stress"[tiab] OR "PTSD"[tiab] OR "post traumatic neuroses"[tiab] OR "posttraumatic neuroses"[tiab] OR "acute stress disorder"[tiab] OR "acute stress disorders"[tiab] OR "reactive attachment disorder"[tiab] OR "reactive attachment disorders"[tiab] OR "disinhibited social engagement disorder"[tiab] OR "disinhibited social engagement disorders"[tiab] OR "anxiety disorder"[tiab] OR "anxiety disorders"[tiab] OR "depressive disorder"[tiab] OR "depressive disorders"[tiab] OR "depression"[tiab] OR "depressions"[tiab] OR "substance related disorder"[tiab] OR "substance related disorders"[tiab] OR "addictive disorder"[tiab] OR "addictive disorders"[tiab] OR "substance addiction"[tiab] OR "substance dependence"[tiab] OR "substance abuse"[tiab]**)**

Search string: Study type

AND ("Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [Publication Type] OR "Systematic Reviews as Topic"[Mesh] OR "Systematic Review" [Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR "Meta-Analysis" [Publication Type] OR "trial"[tiab] OR "randomized"[tiab] OR "randomised"[tiab] OR "randomly"[tiab] OR "systematic review"[ti] OR "systematic reviews"[ti] OR "systematic literature review"[ti] OR "systematic scoping review"[ti] OR "systematic narrative review"[ti] OR "systematic evidence review"[ti] OR "systematic quantitative review"[ti] OR "systematic critical review"[ti] OR "systematic mixed studies review"[ti] OR "systematic mapping review"[ti] OR "Cochrane review"[ti] OR "Cochrane reviews"[ti] OR "systematic search and review"[ti] OR "systematic integrative review"[ti] OR "systematically"[tiab] OR "meta analysis"[ti] OR "meta analyses"[ti] OR "metanalysis"[ti] OR "metanalyses"[ti] OR "metaanalysis"[ti] OR "metaanalyses"[ti] OR "meta review"[ti] OR "meta reviews"[ti] OR "metareview"[ti] OR "metareviews"[ti] OR "umbrella review"[ti] OR "umbrella reviews"[ti]**)**

Search string: Search limits

NOT ("Comment" [Publication Type] OR "Editorial" [Publication Type] OR "Letter" [Publication Type]**) NOT (**"Animals"[Mesh] NOT "Humans"[Mesh]**) AND (**eng[la] OR und[la]**) AND (**2017:2022[dp]**)**

Appendix 4: List of Excluded Studies

List of excluded studies (*n* = 78) by reason for exclusion in Figure 1 PRISMA diagram (Psychedelics: Standalone and combined interventions).

Ongoing study (n = 20)

#	Registry ID	Mental Health Condition	Experimental intervention	Principal Investigator/s	Location	Date of Registration	Expected Completion Date
1	ACTRN12621001358831	Generalised Anxiety Disorder	Psilocybin	Liknaitzky, P.	Australia	2021 (Aug 26)	Not listed (last update May 2022)
2	IRCT20140120016280N5	Obsessive Compulsive Disorder	Ketamine	Hadjighassem, M.	Iran	2021 (May 18)	2023 (Mar 11)
3	IRCT20170413033408N5	Depressive, anxiety and PTSD disorders	Ketamine	Aghilli, B. M. & Mojaveraghili, S. B.	Iran	2021 (Feb 7)	2021 (Oct 22)
4	EUCTR2020-000829-55-DK	Alcohol Use Disorder	Psilocybin	Jensen, M. E.	Denmark	2020 (Oct 27)	Not listed (last update Jul 2021)
5	EUCTR2020-002790-94-SE	Major Depression	Psilocybin	Evengard, J.	Sweden	2020 (Jun 30)	Not listed (last update Nov 2021)
7	EUCTR2015-000222-11-GB	Alcohol Use Disorder	Ketamine	Nil listed.	United Kingdom	2020 (Jul 30)	Not listed (last update Aug 2020)
8	NCT04630964	Major Depression	Psilocybin	Lundberg, J.	Sweden	2020 (Nov 16)	2022 (Dec 31)
9	NCT04620759	Comorbid Major Depression and Alcohol Use Disorder	Psilocybin	Barrett, F. S.	United States	2021 (Apr 14)	2026 (Aug 31)
10	NCT04560660	PTSD	Ketamine	Shiroma, P. R.	United States	2020 (Sep 23)	2024 (Dec 31)
11	NCT04670081/EUCTR2019-003984-24-DE	Treatment-resistant major depression	Psilocybin	Gruender, G.	Germany	2020 (Sep 3)	Not listed (last update Nov 2021)
12	ACTRN12619000311156	Internalising disorders (PTSD, MDD, OCD or phobic disorder)	Ketamine	Glue, P.	New Zealand	2019 (Feb 6)	Not listed (last update Jul 2021)
13	EUCTR2018-004480-31-CZ	Treatment-resistant major depression	Psilocybin	Palenicek, T.	Czech Republic	2019 (Mar 5)	Not listed (last update Apr 2022)
14	ISRCTN10138262	Alcohol Use Disorder	Ketamine	Kamboj, S. & Das, R.	United Kingdom	2019 (Feb 18)	Not listed (last update Jan 2020)
15	NCT04032301	Comorbid PTSD and MDD in Veterans	Ketamine	Krueger, A. & Albott, C. S.	United States	2019 (Jul 25)	2025 (Apr 1)

#	Registry ID	Mental Health Condition	Experimental intervention	Principal Investigator/s	Location	Date of Registration	Expected Completion Date
16	NCT03866252	Major Depression	LSD	Müller, F.	Switzerland	2019 (Mar 7)	2022 (Dec 31)
17	NCT04141501	Alcohol Use Disorder	Psilocybin	Preller, K.	Switzerland	2019 (Oct 28)	2023 (Dec 31)
18	NCT04077437	PTSD	MDMA	Mithoefer, M.	United States	2019 (Sept 4)	2023 (Mar 5)
19	EUCTR2017-003288-36-NL	Treatment-resistant major depression	Psilocybin	Malievskaia, E.	Various	2018 (Jan 24)	Not listed (last update Nov 2021)
20	NCT03153579	Anxiety disorder	LSD	Gasser, P.	Switzerland	2017 (May 15)	2021 (Dec 15)

Ineligible publication type (n = 35)

#	Year	Reference	Exclusion reason
1	2022	Sakurai, H., Yonezawa, K., Tani, H., Mimura, M., Bauer, M., & Uchida, H. (2022). Novel antidepressants in the pipeline (Phase II and III): A systematic review of the US clinical trials registry. *Pharmacopsychiatry, 55*(4), 193-202. https://doi.org/10.1055/a-1714-9097	Review of registries (incomplete trials)
2	2022	Melcer, T., Walker, G. J., Dye, J. L., Walrath, B., MacGregor, A. J., Perez, K., & Galarneau, M. R. (2022). Is prehospital ketamine associated with a change in the prognosis of PTSD? *Military Medicine, 188*(7-8), e2165-e2174. https://doi.org/10.1093/milmed/usac014	Chart review
3	2022	Sarris, J., Pinzon Rubiano, D., Day, K., Galvão-Coelho, N. L., & Perkins, D. (2022). Psychedelic medicines for mood disorders: current evidence and clinical considerations. *Current Opinion in Psychiatry, 35*(1), 22-29. https://doi.org/10.1097/yco.0000000000000759	Narrative review
4	2021	Rucker, J., Jafari, H., Mantingh, T., Bird, C., Modlin, N. L., Knight, G., Reinholdt, F., Day, C., Carter, B., & Young, A. (2021). Psilocybin-assisted therapy for the treatment of resistant major depressive disorder (PsiDeR): Protocol for a randomised, placebo-controlled feasibility trial. *BMJ Open, 11*(12): Article e056091. https://doi.org/10.1136/bmjopen-2021-056091	Feasibility trial
5	2021	Horowitz, M. A., & Moncrieff, J. (2021). Are we repeating mistakes of the past? A review of the evidence for esketamine. *British Journal of Psychiatry, 219*(5), 614-617. https://doi.org/10.1192/bjp.2020.89	Narrative review
6	2021	Gonda, X., Dome, P., Neill, J. C., & Tarazi, F. I. (2021). Novel antidepressant drugs: Beyond monoamine targets. CNS Spectrums, 28(1), 6-15. https://doi.org/10.1017/s1092852921000791	Narrative review
7	2021	Palhano-Fontes, F., Soares, B.L., Galvão-Coelho, N.L., Arcoverde, E., & Araujo, D.B. (2021). Ayahuasca for the treatment of depression. In F. S. Barrett & K. H. Preller (Eds.), Disruptive psychopharmacology (pp. 113-124). Springer. https://doi.org/10.1007/7854_2021_277	Book chapter

#	Year	Reference	Exclusion reason
8	2021	Beaudequin, D., Can, A. T., Jones, M., Yang, C., Scherman, J. K., Dutton, M., Schwenn, P., Forsyth, C. G. G., Jensen, E., Hermens, D. F., & Lagopoulos, J. (2021). Relationships between reduction in symptoms and restoration of function and wellbeing: Outcomes of the Oral Ketamine Trial on Suicidality (OKTOS). *Psychiatry Research, 305*, Article 114212. https://doi.org/10.1016/j.psychres.2021.114212	No control arm
9	2021	Jardim, A. V., Jardim, D. V, Chaves, B. R., Steglich, M., Ot'alora, G. M., Mithoefer, M. C., da Silveira, D. X., Tofoli, L. F., Ribeiro, S., Matthews, R., Doblin, R., & Schenberg, E. E. (2021). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for victims of sexual abuse with severe post-traumatic stress disorder: An open label pilot study in Brazil. *Brazilian Journal of Psychiatry, 43*(2), 181-185. https://doi.org/10.1590/1516-4446-2020-0980	Open label pilot study
10	2021	Mertens, L. J. & Preller, K. H. (2021). Classical psychedelics as therapeutics in psychiatry – Current clinical evidence and potential therapeutic mechanisms in substance use and mood disorders. *Pharmacopsychiatry, 54*(4), 176-190. https://doi.org/10.1055/a-1341-1907	Narrative review
11	2021	Sousa, T. R., Rema, J., Machado, S., & Novais, F. (2021). Psychedelics and hallucinogens in psychiatry: Finding new pharmacological targets. *Current Topics in Medicinal Chemistry, 22*(15), 1250-1260. https://doi.org/10.2174/1568026621666211201145800	Narrative review
12	2020	Monson, C. M., Wagner, A. C., Mithoefer, A. T., Liebman, R. E., Feduccia, A. A., Jerome, L., Yazar-Klosinski, B., Emerson, A., Doblin, R., & Mithoefer, M. C. (2020). MDMA-facilitated cognitive-behavioural conjoint therapy for posttraumatic stress disorder: An uncontrolled trial. *European Journal of Psychotraumatology, 11*(1), Article 1840123. https://doi.org/10.1080/20008198.2020.1840123	No control arm
13	2020	Shiroma, P., McManus, E., Voller, E., Wels, J., Kaler, M., Baltutis, E., Thuras, P. & Erbes, C. (2020). Repeated sub-anesthetic ketamine to enhance prolonged exposure therapy in post-traumatic stress disorder: A proof-of-concept study. *Biological Psychiatry, 87*(9), S217. https://doi.org/10.1016/j.biopsych.2020.02.563	Proof-of-concept study
14	2020	Collins, A. B., Rutter, S. B., & Feder, A. (2020). Development of ketamine administration as a treatment for chronic PTSD. *Psychiatric Annals, 50*(2), 68-76. https://doi.org/10.3928/00485713-20200109-01	Narrative review
15	2020	Yoon, G., Pittman, B., Limoncelli, D., Krystal, J. H., & Petrakis, I. L. (2020). Ketamine has differential effects in individuals with a family history of alcohol use disorder. *Alcoholism: Clinical and Experimental Research, 44*(S1), 70. https://doi.org/10.1111/acer.14355	Conference paper
16	2020	Sloshower, J., Guss, J., Krause, R., Wallace, R. M., Williams, M. T., Reed, S., & Skinta, M. D. (2020). Psilocybin-assisted therapy of major depressive disorder using Acceptance and Commitment Therapy as a therapeutic frame. *Journal of Contextual Behavioral Science, 15*, 12-19. https://doi.org/10.1016/j.jcbs.2019.11.002	Theoretical study

#	Year	Reference	Exclusion reason
17	2020	Feder, A., Rutter, S. B., Schiller, D., & Charney, D. S. (2020). Chapter nine – The emergence of ketamine as a novel treatment for posttraumatic stress disorder. *Advances in Pharmacology, 89*, 261-286. https://doi.org/10.1016/bs.apha.2020.05.004	Book chapter
18	2020	Garakani, A., Murrough, J. W., Freire, R. C., Thom, R. P., Larkin, K., Buono, F. D., & Iosifescu, D. V. (2020). Pharmacotherapy of anxiety disorders: Current and emerging treatment options. *Frontiers in Psychiatry, 11*, Article 595584. https://doi.org/10.3389/fpsyt.2020.595584	Narrative review
19	2020	Glue, P., Neehoff, S., Sabadel, A., Broughton, L., Le Nedelec, M., Shadli, S., McNaughton, N., & Medlicott, N. J. (2020). Effects of ketamine in patients with treatment-refractory generalized anxiety and social anxiety disorders: Exploratory double-blind psychoactive-controlled replication study. *Journal of Psychopharmacology, 34*(3), 267-272. https://doi.org/10.1177/0269881119874457	Not randomised into separate treatment arms
20	2019	Sessa, B., Sakal, C., O'Brien, S., & Nutt, D. (2019). First study of safety and tolerability of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with alcohol use disorder: Preliminary data on the first four participants. *BMJ Case Reports, 12*(7), Article e230109. https://doi.org/10.1136/bcr-2019-230109	Phase 1 trial
21	2019	Duek, O., Levy, I., Yutong, L., Gordon, C., Kelmendi, B., & Harpaz-Rotem, I. (2019). PTSD augmented psychotherapy with ketamine (KPE) – First results. *Biological Psychiatry, 85*(10), S122. https://doi.org/10.1016/j.biopsych.2019.03.305	Conference abstract
22	2019	Dadabayev, A., Liberzon, I., Joshi, S., & Domino, E. (2019). Low dose ketamine infusion for comorbid post traumatic stress disorder and chronic pain. *Neuropsychopharmacology, 44*(Supp 1), 401. https://doi.org/10.1038/s41386-019-0547-9	Conference abstract
23	2019	Feduccia, A. A., Jerome, L., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2019). Breakthrough for trauma treatment: Safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline. *Frontiers in Psychiatry, 10*, Article 650. https://doi.org/10.3389/fpsyt.2019.00650	Narrative review
24	2019	Almond, K. & Allan, R. (2019). Incorporating MDMA as an adjunct in emotionally focused couples therapy with clients impacted by trauma or PTSD. *The Family Journal, 27*(3), 293-299. https://doi.org/10.1177/1066480719852360	Narrative review
25	2019	Griffiths, R., Barrett, F., Darrick, M., Johnson, M., Mary, C., Finan, P., & Davis, A. (2019). Psilocybin-assisted treatment of major depressive disorder: Results from a randomized trial. *Neuropsychopharmacology, 44*(Suppl 1), 439. https://doi.org/10.1038/s41386-019-0547-9	Conference abstract
26	2018	Ivan Ezquerra-Romano, I., Lawn, W., Krupitsky, E., & Morgan, C. J. A. (2018). Ketamine for the treatment of addiction: Evidence and potential mechanisms. *Neuropharmacology, 142*, 72-82. https://doi.org/10.1016/j.neuropharm.2018.01.017	Narrative review
27	2018	Albott, C. S., Lim, K. O., Forbes, M. K., Erbes, C., Tye, S. J., Grabowski, J. G., Thuras, P., Batres-y-Carr, T. M., Wels, J., & Shiroma, P. R. (2018). Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and	Open label trial

#	Year	Reference	Exclusion reason
		treatment-resistant depression. The Journal of Clinical Psychiatry, 79(3), Article 17m11634. https://doi.org/10.4088/JCP.17m11634	
28	2018	Glue, P., Neehoff, S. M., Medlicott, N. J., Gray, A., Kibby, G., & McNaughton, N. (2018). Safety and efficacy of maintenance ketamine treatment in patients with treatment-refractory generalised anxiety and social anxiety disorders. *Journal of Psychopharmacology, 32*(6), 663-667. https://doi.org/10.1177/0269881118762073	No control arm
29	2018	Carhart-Harris, R. L, Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V., & Nutt, D. J. (2018). Psilocybin with psychological support for treatment-resistant depression: Six-month follow-up. *Psychopharmacology, 235*, 399-408. https://doi.org/10.1007/s00213-017-4771-x	Open label trial
30	2017	Glue, P., Medlicott, N. J, Harland, S., Neehoff, S., Anderson-Fahey, B., Le Nedelec, M., Gray, A., & McNaughton, N. (2017). Ketamine's dose-related effects on anxiety symptoms in patients with treatment refractory anxiety disorders. *Journal of Psychopharmacology, 31*(10), 1302-1305. https://doi.org/10.1177/0269881117705089	No control arm
31	2017	Castle, C., Gray, A., Neehoff, S., & Glue, P. (2017). Effect of ketamine dose on self-rated dissociation in patients with treatment refractory anxiety disorders. *Journal of Psychopharmacology, 31*(10), 1306-1311. https://doi.org/10.1177/0269881117725685	Secondary analysis of open-label trial
32	2017	Ionescu, D. (2017). A randomized, double blind, placebo controlled trial of repeat-dose ketamine augmentation for chronic suicidal thinking. *Neuropsychopharmacology, 42*, S5-S6. https://doi.org/10.1038/npp.2017.263	Conference abstract
33	2017	Morgan, C., McAndrew, A., Stevens, T., Nutt, D., & Lawn, W. (2017). Tripping up addiction: The use of psychedelic drugs in the treatment of problematic drug and alcohol use. *Current Opinion in Behavioral Sciences, 13*, 71-76. https://doi.org/10.1016/j.cobeha.2016.10.009	Narrative review
34	2017	McAndrew, A., Lawn, W., Stevens, T., Porffy, L., Brandner, B., & Morgan, C. J. A. (2017). A proof-of-concept investigation into ketamine as a pharmacological treatment for alcohol dependence: Study protocol for a randomised controlled trial. *Trials, 18*, Article 159. https://doi.org/10.1186/s13063-017-1895-6	Proof-of-concept study
35	2017	Dos Santos, R. G., Bouso, J. C., & Hallak, J. E. C. (2017). Ayahuasca, dimethyltryptamine, and psychosis: A systematic review of human studies. *Therapeutic Advances in Psychopharmacology, 7*(4), 141-157. https://doi.org/10.1177/2045125316689030	Systematic review of case reports

Ineligible outcomes (n = 12)

#	Year	Reference	Exclusion reason
1	2021	Meshkat, S., Rodrigues, N. B., Di Vincenzo, J. D., Ceban, F., Jaberi, S., & McIntyre, R. S., Lui, L. M. W., & Rosenblat, J. D. (2021). Pharmacogenomics of ketamine: A systematic review. *Journal of Psychiatric Research, 145*, 27-34. https://doi.org/10.1016/j.jpsychires.2021.11.036	Pharmacogenomics not of interest

#	Year	Reference	Exclusion reason
2	2021	Glue, P., Russell, B., & Medlicott, N. J. (2021). Influence of formulation and route of administration on ketamine's safety and tolerability: Systematic review. *European Journal of Clinical Pharmacology, 77*, 671-676. https://doi.org/10.1007/s00228-020-03047-z	Safety and tolerability only
3	2021	Degerlund Maldi, K., Asellus, P., Myleus, A., & Norstrom, F. (2021). Cost-utility analysis of esketamine and electroconvulsive therapy in adults with treatment-resistant depression. *BMC Psychiatry, 21*, Article 610. https://doi.org/10.1186/s12888-021-03601-8	Economic evaluation
4	2021	Norbury, A., Rutter, S. B., Collins, A. B., Costi, S., Jha, M. K., Horn, S. R., Kautz, M., Corniquel, M., Collins, K. A., Glasgow, A. M., Brallier, J., Shin, L. M., Charney, D. S., Murrough, J. W., & Feder, A. (2021). Neuroimaging correlates and predictors of response to repeated-dose intravenous ketamine in PTSD: Preliminary evidence. *Neuropsychopharmacology*, *46*, 2266-2277. https://doi.org/10.1038/s41386-021-01104-4	Neuroimaging outcomes
5	2021	Diekamp, B., Borentain, S., Fu, D. J., Murray, R., Heerlein, K., Zhang, Q., Schule, C., & Mathews, M. (2021). Effect of concomitant benzodiazepine use on efficacy and safety of esketamine nasal spray in patients with major depressive disorder and acute suicidal ideation or behavior: Pooled randomized, controlled trials. *Neuropsychiatric Disease and Treatment, 17*, 2347-2357. https://doi.org/10.2147/ndt.S314874	Ketamine for depression (established literature)
6	2020	Short, B., Dong, V., Galvez, V., Vulovic, V., Martin, D., Bayes, A. J., Zarate, C. A., Murrough, J. W., McLoughlin, D. M., Riva-Posse, P., Schoevers, R., Fraguas, R., Glue, P., Fam, J., McShane, R., & Loo, C. K. (2020). Development of the Ketamine Side Effect Tool (KSET). *Journal of Affective Disorders, 266*, 615-620. https://doi.org/10.1016/j.jad.2020.01.120	Instrument development study
7	2020	Marseille, E., Kahn, J. G., Yazar-Klosinski, B., & Doblin, R. (2020). The cost-effectiveness of MDMA-assisted psychotherapy for the treatment of chronic, treatment-resistant PTSD. *PLoS ONE*, 15(10), Article e0239997. https://doi.org/10.1371/journal.pone.0239997	Economic evaluation
8	2020	Galvao-Coelho, N. L., de Menezes Galvao, A. C., de Almeida, R. N., Palhano-Fontes, F., Campos Braga, I., Soares, B. L., Maia-De-Oliveira, J. P., Perkins, D., Sarris, J., & De Araujo, D. B. (2020). Changes in inflammatory biomarkers are related to the antidepressant effects of Ayahuasca. *Journal of Psychopharmacology, 34*(10), 1125-1133. https://doi.org/10.1177/0269881120936486	Inflammatory biomarkers
9	2020	Malaca, S., Lo Faro, A. F., Tamborra, A., Pichini, S., Busardo, F. P., & Huestis, M. A. (2020). Toxicology and analysis of psychoactive tryptamines. *International Journal of Molecular Sciences, 21*(23), Article 9279. https://doi.org/10.3390/ijms21239279	Toxicology outcomes
10	2020	Acevedo-Diaz, E. E., Cavanaugh, G. W, Greenstein, D., Kraus, C., Kadriu, B., Zarate, C. A., & Park, L. T. (2020). Comprehensive assessment of side effects associated with a single dose of ketamine in treatment-resistant depression. *Journal of Affective Disorders*, 263, 568-575. https://doi.org/10.1016/j.jad.2019.11.028	Ketamine for depression (established literature)
11	2017	Hirschtritt, M. E, Bloch, M. H, & Mathews, C. A. (2017). Obsessive-compulsive disorder: Advances in diagnosis and treatment. *JAMA, 317*(13), 1358-1367. https://doi.org/10.1001/jama.2017.2200	Diagnosis and treatment rather than outcomes focused

#	Year	Reference	Exclusion reason
12	2017	Papadimitropoulou, K., Vossen, C., Karabis, A., Donatti, C., & Kubitz, N. (2017). Comparative efficacy and tolerability of pharmacological and somatic interventions in adult patients with treatment-resistant depression: A systematic review and network meta-analysis. *Current Medical Research and Opinion,* 33(4), 701-711. https://doi.org/10.1080/03007995.2016.1277201	Search for trials published between 2003 and 2014

Ineligible population (n = 2)

#	Year	Reference	Exclusion reason
1	2021	Bahji, A., Ermacora, D., Stephenson, C., Hawken, E. R., & Vazquez, G. (2021). Comparative efficacy and tolerability of adjunctive pharmacotherapies for acute bipolar depression: A systematic review and network meta-analysis. *The Canadian Journal of Psychiatry, 66*(3), 274-288. https://doi.org/10.1177/0706743720970857	Bipolar disorder
2	2018	Colic, L., Woelfer, M., Colic, M., Leutritz, A. L., Liebe, T., Fensky, L., Sen, Z. D., Li, M., Hoffmann, J., Kretzschmar, M. A., Isermann, B., & Walter, M. (2018). Delayed increase of thrombocyte levels after a single sub-anesthetic dose of ketamine – A randomized trial. *European Neuropsychopharmacology, 28*(6), 701-709. https://doi.org/10.1016/j.euroneuro.2018.03.014	Healthy population

Ineligible intervention (n = 1)

#	Year	Reference	Exclusion reason
1	2021	Steardo (Jr), L., Carbone, E. A., Menculini, G., Moretti, P., Steardo, L., & Tortorella, A. (2021). Endocannabinoid system as therapeutic target of PTSD: A systematic review. *Life, 11*(3), Article 214. https://doi.org/10.3390/life11030214	Cannabis (not included in this report)

Secondary analysis (n = 8)

#	Year	Reference	Exclusion reason
1	2021	Feduccia, A.A., Jerome, L., Mithoefer, M.C. & Holland, J. (2021). Discontinuation of medications classified as reuptake inhibitors affects treatment response of MDMA-assisted psychotherapy. *Psychopharmacology, 238*, 581-588. https://doi.org/10.1007/s00213-020-05710-w	Secondary analysis
2	2021	Rothberg, R. L., Azhari, N., Haug, N. A., & Dakwar, E. (2021). Mystical-type experiences occasioned by ketamine mediate its impact on at-risk drinking: Results from a randomized, controlled trial. *Journal of Psychopharmacology, 35*(2), 150-158. https://doi.org/10.1177/0269881120970879	Secondary analysis
3	2021	Truppman Lattie, D., Nehoff, H., Neehoff, S., Gray, A., & Glue, P. (2021). Anxiolytic effects of acute and maintenance ketamine, as assessed by the Fear Questionnaire subscales and the Spielberger State Anxiety Rating Scale. *Journal of Psychopharmacology, 35*(2), 137-141. https://doi.org/10.1177/0269881120953991	Secondary analysis
4	2021	Ponte, L., Jerome, L., Hamilton, S., Mithoefer, M. C., Yazar-Klosinski, B. B., Vermetten, E., & Feduccia, A. A. (2021). Sleep quality improvements after MDMA-assisted psychotherapy for the treatment of posttraumatic stress disorder. *Journal of Traumatic Stress,* 34(4), 851-863. https://doi.org/10.1002/jts.22696	Secondary analysis

#	Year	Reference	Exclusion reason
5	2021	Jerome, L., Feduccia, A. A., Wang, J. B., Hamilton, S., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2020). Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: A longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology, 237*, 2485-2497. https://doi.org/10.1007/s00213-020-05548-2	Secondary analysis
6	2020	Gorman, I., Belser, A. B., Jerome, L., Hennigan, C., Shechet, B., Hamilton, S., Yazar-Klosinski, B., Emerson, A., & Feduccia, A. A. (2020). Posttraumatic growth after MDMA-assisted psychotherapy for posttraumatic stress disorder. *Journal of Traumatic Stress, 33*(2), 161-170. https://doi.org/10.1002/jts.22479	Secondary analysis
7	2019	Mithoefer, M. C., Feduccia, A. A., Jerome, L., Mithoefer, A., Wagner, M., Walsh, Z., Hamilton, S., Yazar-Klosinski, B., Emerson, A., & Doblin, R. (2019). MDMA-assisted psychotherapy for treatment of PTSD: Study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology, 236*, 2735-2745. https://doi.org/10.1007/s00213-019-05249-5	Secondary analysis
8	2018	Shadli, S. M., Kawe, T., Martin, D., McNaughton, N., Neehoff, S., & Glue, P. (2018). Ketamine effects on EEG during therapy of treatment-resistant generalized anxiety and social anxiety. *International Journal of Neuropsychopharmacology, 21*(8), 717-724. https://doi.org/10.1093/ijnp/pyy032	Secondary analysis

Appendix 5: List of Included Studies

Psychedelic compounds: Standalone and combined interventions (n = 18)

#	Citation	Experimental intervention	Target condition	Combined intervention details (if applicable)
1	Taylor et al. (2018)	Ketamine	SAD	N/A
2	Daly et al. (2021)	Esketamine	Anxiety and TRD	Newly-initiated, open-label, oral antidepressant
3	Dakwar et al. (2018)	Ketamine	CocUD	N/A
4	Dakwar et al. (2017)	Ketamine	CocUD	N/A
5	Dakwar et al. (2019)	Ketamine	CocUD	Mindfulness-based relapse prevention (MBRP)
6	Dakwar et al. (2020)	Ketamine	AUD	Six (6) sessions of motivational enhancement therapy
7	Grabski et al. (2020)	Ketamine	AUD	Seven (7) sessions of manualised relapse-prevention-based psychological therapy or alcohol education (as a placebo control)
8	Abdallah et al. (2022)	Ketamine	PTSD	N/A
9	Feder et al. (2021)	Ketamine	PTSD	N/A
10	Dadabayev et al. (2020)	Ketamine	PTSD	N/A
11	Pradhan et al. (2017)	Ketamine	PTSD	12 sessions of individually tailored, mindfulness-based, trauma-focused psychotherapy (TIMBER)
12	Mitchell et al. (2021)	MDMA	PTSD	3 preparatory and 9 integrative manualised therapy sessions
13	Mithoefer et al. (2018)	MDMA	PTSD	Psychotherapy
14	Ot'alora et al. (2018)	MDMA	PTSD	Psychotherapy
15	Davis et al. (2021)	Psilocybin	MDD	Psychotherapy
16	Carhart-Harris et al. (2021)	Psilocybin	MDD	Psychological support
17	Dos Santos et al. (2021)	Ayahuasca	SAD	N/A
18	Palhano-Fontes et al. (2019)	Ayahuasca	MDD	N/A

Notes. AUD = Alcohol Use Disorder. CocUD = Cocaine Use Disorder. MDD = Major Depressive Disorder. MDMA = Methylenedioxymethamphetamine. N/A = Not applicable. PTSD = Posttraumatic Stress Disorder. SAD = Social Anxiety Disorder. TRD = Treatment-Resistant Depression.

Appendix 6: Matrix of Included Studies

Psychedelic compounds: Standalone and combined interventions (n = 18)

	Anxiety Disorders	Mood/Depressive Disorders	Substance-Related and Addictive Disorders	Trauma- and Stressor-Related Disorders
Ketamine	1 x standalone Tx (SAD) 1 x combined Tx (comorbid anxiety and depression)	established treatment	2 x combined Tx (AUD) 2 x standalone Tx (CocUD) 1 x combined Tx (CocUD)	3 x standalone Tx (PTSD) 1 x combined Tx (PTSD)
MDMA	X	X	X	3 x combined Tx (PTSD)
Psilocybin	X	2 x combined Tx (MDD)	X	X
Ayahuasca	1 x standalone Tx (SAD)	1 x standalone Tx (MDD)		X
LSD	X	X	X	X

Notes. standalone Tx refers to interventions that were not combined with other psychotherapy or pharmacological intervention/s (e.g., antidepressants; mood stabilisers; anti-psychotics). combined Tx refers to interventions that were combined with other psychotherapy or pharmacological intervention/s. X indicates there were no studies included in the analysis for the intervention of interest and the mental health condition/s of interest. AUD = Alcohol Use Disorder. CocUD = Cocaine Use Disorder. MDD = Major Depressive Disorder. MDMA = Methylenedioxymethamphetamine. PTSD = Posttraumatic Stress Disorder. SAD = Social Anxiety Disorder.

Appendix 7: Summary of Findings

1. Ketamine for Social Anxiety Disorder: Standalone Intervention

Citation	Taylor et al. (2018)
Study Design	• Double-blind, randomised, placebo-controlled, trial. • Crossover design.
Sample Size	• 18 participants.
Population	• USA. • Social Anxiety Disorder (SAD; DSM-5 criteria). • Total sample: M = 29.72 years (SD = 11.05); 61.11% male. • Ketamine-first group: M = 30.78 years (SD = 13.50); 77.78% male. • Placebo-first group: M = 28.67 years (SD = 8.66); 44.44% male.
Intervention/s (I) and Comparator/s (C)	• All participants received one IV ketamine infusion and one IV midazolam infusion in a random order with a 28-day washout period between infusions. • I (n = 18): ketamine (0.5 mg/kg) infusion. • C (n = 18): placebo (normal saline) infusion.
Outcome Measure/s	• Liebowitz Social Anxiety Scale (LSAS). • Visual Analog Scale – Anxiety (VAS-Anxiety). • State-Trait Anxiety Inventory – State Subscale (STAI-S). • Hamilton Depression Rating Scale (HAM-D). • Clinician Administered Dissociative States Scale (CADSS).
General	• Participants were recruited through a clinical trials website (www.clinicaltrials.gov), outreach to local anxiety peer support groups, and word of mouth. • Period study was conducted: 2014 to 2016.
Inclusion Criteria	• 18 to 65 years old. • Social Anxiety Disorder (SAD; DSM-5 criteria) as diagnosed by the Structured Clinical Interview for DSM-5 (SCID-5). • Total score greater than (>) 60 on the Liebowitz Social Anxiety Scale (LSAS). • Post-menopausal, surgically sterile, or established birth control (including complete abstinence from sexual intercourse during the trial period). • Stable doses of SSRIs, SNRIs, and clomipramine for at least 2 months prior to study enrolment. • Stable doses of all psychiatric medications for the month prior to treatment. • Discontinuation of PRN anxiety medications (i.e., prescribed “as needed”) for the duration of the study. • Medically and neurologically healthy individuals with stable medical problems and medications (e.g., oral hypoglycaemics) were included if their medications had not been adjusted in the month prior to study entry. • Able to provide written informed consent.
Exclusion Criteria	• Current substance use disorder (excluding tobacco) as diagnosed by the SCID-5 (DSM-5 criteria). • Positive urine toxicology screen for drugs of abuse. • Currently receiving cognitive behavioural therapy.
Assessment Time-Point/s	• Baseline: pre-infusion. • Post-treatment: 3 hours post-infusion. • Follow-up (post-infusion): day 1, 2, 3, 5, 7, 10 and 14.

Citation	Taylor et al. (2018)
Main Findings	• A significantly greater reduction in anxiety symptoms was observed for the ketamine treatment relative to the placebo treatment on the clinician-assessed LSAS ($p = 0.01$) but not on the self-reported VAS-Anxiety ($p = 0.95$). • The proportion of participants who evidenced a treatment response on the LSAS (i.e., > 35% reduction) was significantly higher for the ketamine (n = 6/18; 33.34%) than for the placebo (n = 0/17; 0%) treatment ($p = 0.025$). • The proportion of participants who evidenced a treatment response on the VAS-A (i.e., > 50% improvement) was significantly higher for the ketamine (n = 16/18; 88.89%) than for the placebo (n = 9/17; 52.94%) treatment ($p = 0.034$).

Safety and Adverse Events	• Ketamine demonstrated significantly greater dissociative side effects compared to placebo on the CADSS ($p < 0.01$) that peaked 1-hour post-infusion (1 hour: $p < 0.001$) and dissipated within 2 hours post-infusion (2 hour: $p = 0.99$).
	• All ketamine infusions were completed and were generally well tolerated by participants.
	• The most common side effects of ketamine were:
	o paraesthesia and numbness (n = 9);
	o feeling disconnected from reality (n = 7);
	o vision changes (n = 6);
	o feeling confused/difficulties thinking (n = 6);
	o dizziness (n = 6);
	o distorted sense of time (n = 4);
	o tachycardia > 100 beats per minute (n = 4; max heart rate of 120/min);
	o diastolic hypertension > 90 mmHg (n = 3; max diastolic blood pressure 106 mm Hg);
	o diastolic hypotension < 60 mmHg (n = 2; min diastolic blood pressure 49 mmHg); and
	o systolic hypertension > 160 mmHg (n = 2; max systolic blood pressure 184 mmHg).
	• All side effects resolved within 2 hours post-infusion.

2. Esketamine for Comorbid Anxiety and Treatment-Resistant Depression: Combined Intervention (Pharmacological)

Citation	Daly et al. (2021)
Study Design	• Double-blind, randomised, placebo-controlled, trial. • Multi-site.
Sample Size	• 223 participants (per protocol sample). o 227 participants randomised. o 4 participants excluded due to protocol deviations: 3 participants did not receive any study drug; 1 participant did not receive a dose of study antidepressant.
Population	• USA. • Comorbid anxiety (unspecified) and MDD (DSM-5 criteria). • Treatment resistant. • Esketamine group: M = 44.9 years (SD = 12.91); 61.5% male. • Placebo group: M = 45.4 years (SD = 11.09); 60.8% male.
Intervention/s (I) and Comparator/s (C)	• All participants received a newly-initiated, open-label, oral antidepressant (daily). • All participants received a nasal spray (twice weekly for 4 weeks).

Citation	Daly et al. (2021)
	• I (n = 114): esketamine (56 mg or 84 mg). • C (n = 109): placebo (saline).
Outcome Measure/s	• Montgomery-Asberg Depression Rating Scale (MADRS). • Generalized Anxiety Scale, 7-item (GAD-7). • Clinician Administered Dissociative States Scale (CADSS).
General	• This study presents a post-hoc data analysis for participants with comorbid anxiety who were part of the TRANSFORM-2 clinical trial. • The TRANSFORM-2 trial recruited outpatients with treatment-resistant depression: participants were randomised to receive either esketamine or placebo nasal spray in combination with a newly-initiated, open-label, oral antidepressant (see Popova et al., 2019: original paper excluded as established literature). • At baseline, 72.6% (n = 162/223) of participants had either comorbid anxiety symptoms or an anxiety disorder: o 13.5% (n = 30/223) of participants met criteria for current anxiety disorder on the Mini International Neuropsychiatric Interview (MINI) at screening; and o 69.1% (n = 154/223) of participants had a total score of at least (≥) 10 on the GAD-7 at both screening and baseline. • Period study conducted: not reported.
Inclusion Criteria	• Documented non-response to at least (≥) one (1) but no more than (≤) five (5) oral antidepressants based on historical report and the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ). • Adherence to the newly-initiated, open-label, oral antidepressant for a minimum of two (2) weeks from study entry, continued prospectively for an additional four (4) weeks during a screening/observational phase, prior to combined treatment with the esketamine/placebo nasal spray.
Exclusion Criteria	• Moderate-to-severe alcohol or substance use disorder in the most recent 6-month period. • Current diagnosis of obsessive-compulsive disorder. • Total daily dose of benzodiazepines equivalent to greater than (>) 6 mg/day of lorazepam.
Assessment Time-Point/s	• Baseline. • Day 2, 8, 15, 22, and 28.
Main Findings	• At post-treatment: o A significantly greater improvement in depressive symptoms (as measured by the MADRS) was observed for participants in the esketamine + antidepressant group compared with those in the placebo + antidepressant group (without comorbid anxiety: p = .017; with comorbid anxiety: p = .036). o The improvement in depressive symptoms did not significantly differ for participants with/without anxiety (p = .371). o There was a greater likelihood of meeting criteria for treatment response in the esketamine + antidepressant group compared with the antidepressant + placebo group (with comorbid anxiety: 65.3% vs. 54.2%, respectively; without comorbid anxiety: 79.3% vs. 46.4%, respectively). o There was a greater likelihood of achieving remission in the esketamine + antidepressant group compared with the placebo + antidepressant group (with comorbid anxiety: 47.2% vs. 33.3%, respectively; without comorbid anxiety: 65.5% vs. 25.0%, respectively).

Citation	Daly et al. (2021)
	○ Treatment response (p = .136) and remission (p = .088) did not significantly differ for participants with/without anxiety.
Safety and Adverse Events	• Nine participants discontinued the study due to an adverse event: ○ Esketamine group (n = 8/114; 7.0%). ○ Placebo group (n = 1/109; 0.9%).

3. Ketamine for Cocaine Use Disorder: Standalone Intervention

Citation	Dakwar et al. (2018)
Study Design	• Double-blind, randomised, active-controlled, trial. • Crossover design.
Sample Size	• 18 participants (per protocol sample). ○ 20 participants randomised. ○ 2 participants excluded due to missing outcome data.
Population	• USA. • Cocaine dependence (not explicitly defined by the authors). • Not treatment seeking: disinterested in treatment or abstinence. • 55.6% male.
Intervention/s (I) and Comparator/s (C)	• Inpatient Phase 1: all participants received one IV sham infusion (saline over 52 minutes). • Inpatient Phase 2 and 3: all participants received one IV ketamine infusion and one IV midazolam infusion in a random order. • I (n = 20): ketamine hydrochloride. ○ 1 x 2-minute bolus of ketamine (0.11 mg/kg IV infusion); and ○ 1 x 50-minute infusion of ketamine (0.60 mg/kg) in saline. • C (n = 20): midazolam. ○ 1 x 2-minute bolus of saline; and ○ 1 x 50-minute infusion of midazolam (0.025 mg/kg) in saline.
Outcome Measure/s	• Clinician Administered Dissociative States Scale (CADSS). • Hood's Mysticism Scale (HMS). • Near-Death Experiences Scale (NDES). • Global Improvement Score (0 to 100%) across 3 domains: ○ cocaine self-administration (in hospital). ○ craving (in the natural ecology). ○ cocaine use (in the natural ecology).
General	• Sample baseline characteristics: history of PTSD (n = 3; 16.8%); comorbid alcohol use disorder (n = 2; 11.2%); cocaine use (days in past month: 9.4; SD = 7.1); cocaine amount (cost per day: $49.82; SD = $32.21). • Participants were hospitalised up to 3 times (6 days per admission) in a controlled research unit. • Each admission was separated by two weeks to control for carryover effects and to assess cocaine use in the natural ecology. • Each 6-day hospitalisation involved: ○ an initial 2-day washout period; ○ a 28-minute 'sample session' on day 3 when two obligatory free-base cocaine doses (25 mg) were smoked to allow for assignment of value to the research cocaine and to intensify craving; ○ a 52-minute intravenous infusion on day 4; ○ a 70-minute 'choice session' of five choices (25 mg cocaine vs $11) on day 5; and

Citation	Dakwar et al. (2018)
	o discharge on day 6. • During the first hospitalisation, all participants received an infusion of normal saline to identify, and exclude from the research, individuals who did not robustly choose cocaine prior to the active infusions (less than two choices out of five). • Period study was conducted: not reported.
Inclusion Criteria	• Cocaine dependent (not explicitly defined by the authors). • Disinterested in treatment or abstinence. • Medically healthy.
Exclusion Criteria	• Physiological dependence on opioids, alcohol, or benzodiazepines. • History of psychotic or dissociative symptoms. • Current symptoms indicative of an anxiety or depressive disorder (DSM-IV criteria). • Family history of psychosis (first-degree relative). • Obesity (BMI > 35). • Cardiovascular or pulmonary disease.
Assessment Time-Point/s	• Baseline. • Day 5 of each 6-day admission (up to three 6-day admissions separated by two weeks): 70-minute 'choice session' of five choices (25 mg cocaine vs. $11). • Follow-up: three times per week for two weeks following each 6-day admission.
Main Findings	• Significantly higher global improvement scores were observed for ketamine [M = 56%, SE = 7%] compared with midazolam [M = 20.7%, SE = 3.8%] treatment ($p < 0.001$). • Mediation analysis was performed by treating participants as random effects and placing all psychoactive variables (HMS, NDES and CADSS scores), along with dose of ketamine received (0 to 70.5 mg, ketamine vs. midazolam), into a single multivariate analysis, with global improvement score as the dependent variable. o HMS score was the only significant mediator ($p = 0.0175$). o Ketamine dose was not significant ($p = 0.0562$) supporting mediation. o The total indirect effect was 0.2029 (0.5676 to 0.3647), which explained 35.7% (0.2029/0.5676) of the total treatment effect. • Significantly higher levels of all psychoactive effects (as measured by CADSS, HMS and NDES) were observed for ketamine compared with midazolam treatment. o Significantly higher HMS scores were observed for ketamine [M = 103, SE = 7.8] compared with midazolam [M = 63, SE = 9.8] treatment ($p < 0.001$). o Significantly higher NDES scores were observed for ketamine [M = 10.7, SE = 1.6] compared with midazolam [M = 4.3, SE = 0.8] treatment ($p < 0.001$). o Significantly higher CADSS scores were observed for ketamine [M = 24.5, SE = 3.4] compared with midazolam [M = 4.9, SE = 1.2] treatment ($p < 0.001$).
Safety and Adverse Events	All participants tolerated the study procedures without adverse events (i.e., no unexpected psychiatric disturbances; no initiation of ketamine or benzodiazepine misuse).

4. Ketamine for Cocaine Use Disorder: Standalone Intervention

Citation	Dakwar et al. (2017)
Study Design	• Double-blind, randomised, active-controlled, trial. • Crossover design.
Sample Size	• 20 participants (per protocol sample). o 26 participants randomised. o 6 participants excluded due to protocol deviations.
Population	• USA • Cocaine Use Disorder (DSM-IV criteria). • Not treatment seeking. • Total sample: M = 48.6 years (SD = 6.1); 55% male.
Intervention/s (I) and Comparator/s (C)	• Inpatient Phase 1: all participants received one IV sham infusion (saline over 52 minutes). • Inpatient Phase 2 and 3: all participants received one IV ketamine infusion and one IV midazolam infusion in a random order. • I (n = 20): ketamine hydrochloride. o 1 x 2-minute bolus of ketamine (0.11 mg/kg IV infusion); and o 1 x 50-minute infusion of ketamine (0.60 mg/kg) in saline. • C (n = 20): midazolam. o 1 x 2-minute bolus of saline; and o 1 x 50-minute infusion of midazolam (0.025 mg/kg) in saline.
Outcome Measure/s	• Number of cocaine self-administration choices (around 28 hrs post-infusion compared with baseline). • Urine toxicology (drug use). • Various assessments and questionnaires (unspecified) pertaining to cocaine craving, reactivity, and medication side effects. • Five Facet Mindfulness Questionnaire (FFMQ). • Clinician Administered Dissociative Symptoms Scale (CADSS).
General	• Sample baseline characteristics: cocaine use (days in past month: 9.8; SD = 7.2); cocaine amount (cost per day: $46.88; SD = $30.74). • Participants were hospitalised up to three times (6 days per admission) in a controlled research unit. • Each admission was separated by two weeks to control for carryover effects and to assess cocaine use in the natural ecology. • Each 6-day hospitalisation involved: o an initial 2-day washout period; o a 28-minute 'sample session' on day 3 when two obligatory free-base cocaine doses (25 mg) were smoked to allow for assignment of value to the research cocaine and to intensify craving; o a 52-minute intravenous infusion on day 4; o a 70-minute 'choice session' of five choices (25 mg cocaine vs. $11) on day 5; and o discharge on day 6. • During the first hospitalisation, all participants received an infusion of normal saline to identify, and exclude from the research, individuals who did not robustly choose cocaine prior to the active infusions (at least three choices out of five). • Period study was conducted: not reported.
Inclusion Criteria	• 21 to 55 years old. • Cocaine dependent individuals (minimum use criteria: at least two occasions of free-base cocaine use per week; > $40 per use).

Citation	Dakwar et al. (2017)
	• Medically healthy.
Exclusion Criteria	• Physiological dependence on certain other substances (opioids, alcohol, benzodiazepines). • History of abuse of or adverse reaction to ketamine or benzodiazepines. • History of psychotic or dissociative symptoms. • Current symptoms indicative of a depressive or anxiety disorder (DSM-IV criteria). • First-degree family history of psychosis. • Obesity (BMI > 35). • Cardiovascular or pulmonary disease.
Assessment Time-Point/s	• Baseline. • Day 5 of each 6-day admission (up to three 6-day admissions separated by two weeks): 70-minute 'choice session' of five choices (25 mg cocaine vs. $11). • Follow-up: three times per week for two weeks following each 6-day admission.
Main Findings	• Significant reductions in rates of cocaine self-administration were observed for ketamine [M = 1.61] compared with midazolam [M = 4.33] treatment [t (17) = 5.43, p < 0.0001]. • Significant improvements in non-reactivity rates (maximum score of 5) were observed for ketamine [M = 3.46] compared with midazolam [M = 2.92] treatment [t (17) = -2.39, p < 0.05]. • Significant reductions in cocaine use ($ in the natural ecology over the preceding 3-day period) were initially observed for ketamine [M = $22.45] compared with midazolam [M = $3.20] treatment [t (17) = 2.97, p < 0.05], but not at subsequent time points. • Significant reductions in cocaine craving were observed for ketamine [59.6%] compared with midazolam [15.3%] treatment prior to discharge [t (17) = 3.44, p < 0.01], but not at subsequent time points. • More participants were voluntarily abstinent in the ketamine treatment (n = 2/10) compared with the midazolam treatment (n = 0/10) following Phase 2.
Safety and Adverse Events	• All participants tolerated the study procedures without notable adverse events. • Ketamine led to acute dissociation that resolved within 30 minutes post-infusion. • There were no persistent dissociative or other adverse events.

5. Ketamine for Cocaine Use Disorder: Combined Intervention (Psychotherapy)

Citation	Dakwar et al. (2019)
Study Design	• Single-blind, randomised, active-controlled, trial.
Sample Size	• 55 participants (intention-to-treat sample). o 7 participants discontinued or lost contact in the ketamine group o 16 participants discontinued or lost contact in the midazolam group.
Population	• USA. • Cocaine dependence (DSM-IV criteria). • Treatment seeking. • Total sample: M = 47.0 years (SD = 9.3); 74.5% male. • Ketamine group: M = 45.0 years (SD = 7.1); 81.5% male. • Midazolam group: M = 48.9 years (SD = 11.0); 67.9% male.

Citation	Dakwar et al. (2019)
Intervention/s (I) and Comparator/s (C)	• All participants received eight mindfulness-based relapse prevention (MBRP) sessions (week 1: 4 sessions post-infusion on day 2 to 5; week 2 to 5: one session per week for 4 weeks). • All participants received one (40-minute) IV infusion on day 2 of week 1. • I (n = 27): ketamine (0.5 mg/kg). • C (n = 28): midazolam (0.025 mg/kg).
Outcome Measure/s	• Timeline Followback (TLFB) method for self-reported drug use (cocaine and other drugs including alcohol, tobacco, benzodiazepines, and ketamine). • Urine toxicology. • Cocaine-related vulnerabilities such as craving (visual analogue scale). • Five-Facet Mindfulness Questionnaire. • Perceived Stress Scale.
General	• Median baseline cocaine use ($/day) was $32.86 in the ketamine group and $36.43 in the midazolam group. • To minimise expectancy effects, participants were told that they might receive any of several medications: amantadine, buspirone, D-cycloserine, ketamine, memantine, midazolam, or saline. • Period study was conducted: September 2011 to December 2016.
Inclusion Criteria	• Adults under (<) 70 years of age. • Medically healthy. • Cocaine dependent (DSM-IV criteria). • Met minimum cocaine use criteria over the 4-week period preceding screening (i.e., one occasion of cocaine use per week at >$200; two occasions of cocaine use per week at >$40 each time; or three or more occasions of cocaine use a week at any amount; and urine toxicology indicative of cocaine use on at least one occasion during screening). • No psychiatric comorbidity.
Exclusion Criteria	• Individuals with a history of psychotic or dissociative symptoms. • Current symptoms indicative of an anxiety or depressive disorder (DSM-IV criteria). • Benzodiazepine or opioid use (DSM-IV) disorder.
Assessment Time-Point/s	• During treatment: twice weekly for four weeks (week 2 to 5; outpatient phase). • Follow up: 6 months.
Main Findings	• For end-of-study abstinence, the proportion of participants with urine-test-confirmed abstinence over the last 2 weeks of the study was higher in the ketamine group (48.2%; 13/27) compared with the midazolam group (10.7%; 3/28). • After controlling for route of use, end-of-study abstinence was significantly (5.7 times) higher in the ketamine group than in the midazolam group (OR = 5.7; 95% CI = 1.3 to 25.1; $\chi 2$ (1) = 5.34, p = 0.02). • After controlling for route of use, the ketamine group was significantly (53%) less likely to relapse (dropout or use cocaine) compared with the midazolam group (hazard ratio = 0.47; 95% CI = 0.24 to 0.92; p = 0.03). • After controlling for route of use, cocaine use was significantly (7.8 times) higher in the midazolam group than in the ketamine group (OR = 7.8; 95% CI = 1.5 to 39.9; t (164) = 2.50, p = 0.01). • After controlling for route of use, cocaine craving scores were significantly (58.1%) lower in the ketamine group compared with the midazolam group (t (100) = -2.57; 95% CI = 18.6 to 78.6; p = 0.01).

Citation	Dakwar et al. (2019)
	• There was no significant change in drug use over time in either group (t (164) = -0.29, p = 0.77), suggesting that participants in the ketamine group maintained their early gains throughout the trial. • There was no significant change in craving scores over time for either group (t (100) = -1.59, p = 0.11); suggesting that early improvements in craving observed for the ketamine group were sustained over time. • At the 6-month follow-up (telephone interview), 44% (n = 12/27) of the participants in the ketamine group reported that they were abstinent compared with none of the participants in the midazolam group. That is, abstinence was significantly associated with ketamine treatment ($\chi 2$ (1) = 15.92, p < 0.001).
Safety and Adverse Events	• Physicians examined participants for adverse events unique to the study medications, such as persistent psychoactive effects and the emergence of ketamine or benzodiazepine misuse. • The only reported adverse event was mild sedation lasting no longer than 12 hours (reported in seven participants in the midazolam group and three in the ketamine group). • There were no instances, in either group, of persistent psychiatric disturbances, clinical worsening, increased drug use, or emergence of new drug misuse (ketamine, opioids, or benzodiazepines), as assessed by self-report, urine toxicology, and psychiatric assessments.

6. Ketamine for Alcohol Use Disorder: Combined intervention (Psychotherapy)

Citation	Dakwar et al. (2020)
Study Design	• Single-blind, randomised, active-controlled, trial.
Sample Size	• 40 participants (intention-to-treat sample). o 6 participants from the midazolam group discontinued or lost contact with trial.
Population	• USA. • Alcohol Dependence (DSM-IV criteria). • Treatment seeking. • Total sample: M = 53.0 years (SD = 9.8); 47.5% male. • I (ketamine): M = 50.4 years (SD = 11.3); 58.8% male. • C (midazolam): M = 55 years (SD = 8.3); 39.1% male.
Intervention/s (I) and Comparator/s (C)	• All participants received six motivational enhancement therapy sessions over five weeks. • All participants received one (50-minute) IV infusion on a “quit day” during the second week of the study. • I (n = 17): ketamine hydrochloride. o 1 x 2-minute (0.11 mg/kg) bolus; and o 1 x 50-minute IV infusion (0.6 mg/kg). • C (n = 23): midazolam. o 1 x 2-minute saline bolus; and o 1 x 50-minute IV infusion (0.025 mg/kg).
Outcome Measure/s	• Primary: o Timeline Followback (TLFB; self-reported number of drinks per calendar day since last clinic visit).

Citation	Dakwar et al. (2020)
	○ Urine ethyl glucuronide test: a positive test for participants who reported abstinence since last clinic visit led to the days being marked as drinking days. • Secondary: ○ Average number of drinks per day. ○ Hamilton Depression Rating Scale (HAM-D). ○ Five Facet Mindfulness Questionnaire (FFMQ). ○ Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar). ○ Perceived Stress Scale (PSS); modified version. ○ Behavioral Inhibition System (BIS). ○ Barrett Impulsiveness Scale (BIS-11). ○ Alcohol Abstinence Self-Efficacy Scale (AASE). ○ Drug-Taking Confidence Questionnaire (DTCQ). ○ Craving and arousal assessed with Visual analogue scale (VAS).
General	• Alcohol and other drug use were determined by self-report and urine toxicology. • To minimise expectancy effects, participants were informed that they might receive any of several medications, in addition to ketamine or midazolam. • Period study was conducted: September 2014 to September 2017. • Secondary analyses in other papers: Rothberg, Azhari, Haug et al. (2020).
Inclusion Criteria	• Adults less than (<) 70 years of age. • No medical illness or psychiatric comorbidity. • Diagnosis of alcohol dependence (DSM-IV criteria) and minimum daily use (at least four heavy drinking days over the past 7 days) or weekly use (35 drinks per week for men and 28 drinks per week for women). • Not using other substances.
Exclusion Criteria	• History of severe withdrawal symptoms (e.g., seizures, cardiac instability, and delirium). • History of psychotic or dissociative symptoms. • Current symptoms indicative of a depressive disorder (DSM-IV criteria).
Assessment Time-Point/s	• Baseline. • During treatment: two visits per week (separated by 3 to 4 days); except week 2 (infusion week): 3 visits on 3 consecutive days. • Follow-up: 6 months post-treatment (via phone).
Main Findings	• Alcohol abstinent days increased in both groups over time [$F(1, 797) = 8.21$, $p = 0.004$]. • Ketamine significantly increased the likelihood of abstinence compared with midazolam ($p < 0.001$). • This between-group difference was not significant when the analysis was adjusted for total baseline drinks ($p = 0.297$). • The time-to-relapse (defined as first heavy drinking day or study dropout) was significantly longer in the ketamine group compared with the midazolam group ($p = 0.04$). • However, there were no significant between-group differences in the time to first use, or the time to the first heavy drinking day. • The probability of a heavy drinking day increased with each (post-infusion) day for the midazolam group ($p = 0.001$), but not the ketamine group ($p = 0.74$). • No significant between-group differences on the secondary outcomes (craving, withdrawal, self-efficacy, mindfulness, stress sensitivity, and impulsivity) were observed for the ketamine group compared with the midazolam group.

Citation	Dakwar et al. (2020)
	• For the participants who were contactable at the 6-month follow-up (ketamine group: n = 8; midazolam group: n = 11), abstinence was reported by 75% (n = 6/8) of the ketamine group and 27% (n = 3/11) of the midazolam group.
Safety and Adverse Events	• Infusions were generally well tolerated. • The most common adverse events were sedation (midazolam: n = 12; ketamine: n = 8) and headache (midazolam: n = 4; ketamine: n = 6), which persisted for approximately 12 hours post-infusion. • Immediately following infusion, scores on the Clinician-Administered Dissociative States Scale (CADSS) were significantly higher in the ketamine group [median = 19, interquartile range: 9 – 30.75] compared with the midazolam group [median = 2; interquartile range = 0.25 to 9.25; $\chi 2 = 7.87$, p = 0.005]. • Two participants in the ketamine group experienced mild agitation lasting one-hour post-infusion. • There were no incidents of persistent psychoactive effects, or initiation of drug misuse (benzodiazepines, opioids, or ketamine), in either study group.

7. Ketamine for Alcohol Use Disorder: Combined Intervention (Psychotherapy)

Citation	Grabski et al. (2022)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 96 participants (intention-to-treat sample). o 15 participants discontinued treatment. o 14 participants were lost to follow up.
Population	• United Kingdom. • Alcohol Dependence (DSM-IV/DSM-5 criteria). • Total sample: M = 44.07 years (SD = 10.59); 63.54% male. o I (ketamine + PT): M = 45.2 years (SD = 8.7); 58% male. o I (ketamine + AE): M = 40.5 years (SD = 11.1); 71% male. o C (placebo + PT): M = 47.0 years (SD = 11.8); 65% male. o C (placebo + AE): M = 43.7 years (SD = 10.2); 60% male.
Intervention/s (I) and Comparator/s (C)	• All participants received psychotherapy of either manualised (relapse-prevention-based) Psychological Therapy (PT; intervention) or Alcohol Education (AE; control) from visit 2 to visit 8 (over 8 weeks). • All participants received three (40-minute) IV infusions spaced one to three weeks apart of either ketamine (0.8mg/kg) or saline (0.9%). • I (n = 24): ketamine + PT. o Discontinued treatment (n = 6). o Lost to follow-up (n = 4). • I (n = 24): ketamine + AE. o Discontinued treatment (n = 4). o Lost to follow-up (n = 4). • C (n = 23): placebo + PT. o Discontinued treatment (n = 3). o Lost to follow-up (n = 3). • C (n = 25): placebo + AE. o Discontinued treatment (n = 2). o Lost to follow-up (n = 3).
Outcome Measure/s	• Primary:

Citation	Grabski et al. (2022)
	○ Self-reported percentage days abstinent at 6 months using the Timeline Followback (TLFB) method. ○ Confirmed alcohol relapse 6 months after first infusion. • Secondary: ○ Self-reported relapse and percentage days abstinent at 3 months. ○ Beck Depression Inventory (BDI). ○ Hamilton Depression Rating Scale (HAM-D). ○ Short Form Survey, 12-item (SF-12). ○ Psychotomimetic States Inventory. ○ Fagerstrom Test for Nicotine Dependence. ○ Alcohol Craving Questionnaire.
General	• All participants had to achieve initial abstinence at randomisation, meaning that they had to be abstinent for at least 24 hours and have a reading of 0.0 on a breath alcohol test at the baseline visit. • Participants were also required to have the goal of abstinence for at least the 6-month duration of the trial. • At screening, participants reported drinking an average of 34.5 UK standard units per week (SD = 34.4) and 8.2 quit attempts (SD = 16.3). • Period study was conducted: September 2016 to July 2019.
Inclusion Criteria	• 18 to 65 years old. • DSM-5 criteria for moderate to severe AUD, or DSM-IV criteria for AUD within the last 12 months. • English language proficiency. • Currently abstinent from alcohol including negative urine screen for all drugs apart from cannabis and benzodiazepines. • Willing to wear SCRAM-X bracelet for active treatment. • Willing to use an effective method of contraception from the time consent is signed until 6 weeks after treatment discontinuation; and negative pregnancy test within 7 days prior to registration and on day one of treatment.
Exclusion Criteria	• Diagnosis of any current or past psychiatric disorder (except for depression, anxiety, AUD, or alcohol dependence) or of substance dependence (except for AUD, cannabis, and benzodiazepines). • Previous help-seeking or professional help for dependence on an illicit substance. • Uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg and diastolic blood pressure > 90 mmHg). • Use of antihypertensives or antidepressants. • Current suicidal ideation. • More than 10 previous inpatient alcohol detoxifications. • History of harmful ketamine use. • BMI outside normal limits (i.e., < 16 and > 35). • Any relevant physical health issues, or medication use that may pose risk when combined with ketamine (as determined by medically qualified personnel).
Assessment Time-Point/s	• Screening (1-28 days before visit 1). • Baseline (1-28 days before visit 1). • Treatment phase: ○ 1 to 5 days after visit 2. ○ 4 to 21 days after visit 2. ○ 1 to 5 days after visit 4. ○ 4 to 21 days after visit 4. ○ 1 to 5 days after visit 6. ○ 4 to 21 days after visit 6.

Citation	Grabski et al. (2022)
	• Follow-up: o 11 to 13 weeks after visit 2. o 23 to 25 weeks after visit 2.
Main Findings	• At the 6-month follow-up, a significant higher percentage of days abstinent from alcohol was observed for the ketamine group compared with the placebo group across therapy groups [M(diff) = 10.1; 95% CI = 1.1 to 19.0]. • The greatest reduction was observed in the ketamine plus therapy group compared with the saline plus education group [M(diff) = 15.9, 95% CI = 3.8 to 28.1]. • No significant difference was found for relapse (recurrent heavy use) within 6 months. • No significant difference in percentage of days abstinent, or odds of relapse, was observed for the ketamine plus therapy condition compared with the ketamine plus education condition. • A significant reduction in depressive symptoms (as measured by the BDI) was observed for the ketamine group compared with the placebo group at 3 months [M(diff) = -2.6, 95% CI = -4.9 to -0.4]; however, this was not maintained at the 6-month follow-up. • No significant differences in depressive symptoms (as measured by HAM-D) at both the 3- or 6-month follow-up was observed across groups.
Safety and Adverse Events	• 53 adverse events in 20 participants were rated by medical staff as either: definitely (n = 57), probably (n = 53), or possibly (n = 43), related to the study drug. • None of these were rated as serious adverse events, and the majority were rated as mild. • Four adverse events in three participants were rated as severe (i.e., significant symptoms that prevent normal daily activity): all in the active drug condition (low mood, hypertension, tachycardia, and euphoria). • Two participants in the active drug condition withdrew because they could not tolerate the treatment.

8. Ketamine for Posttraumatic Stress Disorder: Standalone Intervention

Citation	Abdallah et al. (2022)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 158 participants.
Population	• USA. • PTSD (DSM-5 criteria). • Treatment resistant. • Veterans and service members (18 to 70 years old). • I (standard-dose ketamine): M = 43.2 years (SD = 12.7); 74.5% male. • I (low-dose ketamine): M = 45.2 years (SD = 11.2); 81.1% male. • C (placebo): M = 42.0 years (SD = 10.8); 74.1% male.
Intervention/s (I) and Comparator/s (C)	• All participants received eight (40-minute) IV infusions (two per week for four weeks). • I (n = 51): standard-dose ketamine (0.5 mg/kg). • I (n = 53): low-dose ketamine (0.2 mg/kg). • C (n = 54): placebo (saline).
Outcome Measure/s	• PTSD Checklist for DSM-5 (PCL-5; self-report).

Citation	Abdallah et al. (2022)
	• Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). • Montgomery-Asberg Depression Rating Scale (MADRS). • Clinician-Administered Dissociative State Scale (CADSS). • Positive and Negative Syndrome Scale (PANSS).
General	• Treatment response was defined as at least (≥) 25% improvement in CAPS-5 score following treatment relative to baseline. • Period study was conducted: September 2016 to March 2020.
Inclusion Criteria	• 18 to 70 years old. • Veterans and service members. • PTSD diagnosis based on a structured CAPS-5 interview. • CAPS-5 score of at least (≥) 23 (i.e., moderate to severe PTSD). • Non-response to at least one (1) adequate trial of an FDA-approved antidepressant (for PTSD or depression) as determined by Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ). • Not medicated, or stable on antidepressant medication for at least 4 weeks, or PTSD-focused psychotherapy for at least 6 weeks. • If female, not pregnant or breastfeeding, and on a medically-acceptable contraceptive. • Resting blood pressure higher than 90/60 mmHg and lower than 150/90 mmHg. • Heart rate higher than 45/minute and lower than 100/minute. • Able to read, write, and provide written informed consent in English.
Exclusion Criteria	• Psychotic disorder or features, or manic or mixed episodes. • Unstable medical condition. • Suicidal or homicidal risk meriting crisis intervention. • Severe brain injury. • Moderate or severe substance use disorder (within last 3 months) except mild to moderate alcohol use disorder (with negative breathalyser). • Currently using monoamine oxidase inhibitors, memantine, or long-acting benzodiazepines; or a known sensitivity to ketamine.
Assessment Time-Point/s	• Baseline. • During treatment (prior to each infusion, at 24 hours post-first and post-last infusion). • End of treatment (weekly for 4 weeks after last infusion).
Main Findings	• PTSD symptoms (as measured by the PCL-5). o Improved over time for all study groups (standard dose; low dose; placebo): significant effect of time [F (9,133) = 37.1, p < 0.0001]; no significant effect of treatment [F (2,148) = 1.8, p = 0.17]; no significant treatment-by-time interaction [F (18,137) = 1.1, p = 0.38]. o Standard dose compared to placebo. ▪ 24 hrs post-first infusion: no significant reduction in PCL-5 scores [M(diff) = 6.6, SEM = ±3.1, t (149) = 2.1, p = 0.04, adj. p = 0.11]. ▪ End of treatment: no significant reduction in PCL-5 scores [M(diff) = 5.0, SEM = ± 3.4, t (147) = 1.5, p = 0.14, adj. p = 0.28]. o Low dose compared to placebo. ▪ 24 hrs post-first infusion: no significant reduction in PCL-5 scores [M(diff) = 3.3, SEM = ± 3.1, t (149) = 0.3, p = 0.29, adj. p = 0.57]. ▪ End of treatment: no significant reduction in PCL-5 scores [M(diff) = 6.4, SEM = ± 3.3, t (147) = 2.0, p = 0.05, adj. p = 0.16]. o Standard dose compared to low dose.

Citation	Abdallah et al. (2022)
	▪ No significant difference in PCL-5 scores [p > 0.2, adj. p > 0.5]. o The percentage of responders showing at least (≥) 25% improvement in PCL-5 scores at 24 hrs post-first infusion was higher in the intervention groups (standard dose: 47%; low dose: 47%; placebo: 33%) but the difference was not significant [$\chi 2$ (2) = 5.0, p = 0.08]. • PTSD symptoms (as measured by the CAPS-5). o Improved over time for all groups (standard dose; low dose; placebo): significant effect of time [F (1,124) = 103.4, p < 0.0001]; no significant effect of treatment [F (2,145) = 0.8, p = 0.46]; no significant treatment-by-time interaction [F (2,124) = 2.7, p = 0.07]. o Standard dose compared to placebo. ▪ Follow up (4 weeks post-last infusion): no significant reduction in CAPS-5 scores [M(diff) = 4.7, SEM = ± 2.8, t (124) = 1.7, p = 0.09, adj. p = 0.18]. o Low dose compared to placebo. ▪ Follow up (4 weeks post-last infusion): no significant reduction in CAPS-5 scores [M(diff) = 6.0, SEM = ± 2.7, t (124) = 2.2, p = 0.03, adj. p = 0.09]. o Standard dose compared to low dose. ▪ No significant difference in CAPS-5 scores [p = 0.65, adj. p = 0.65].
Safety and Adverse Events	• Most participants (87%; n = 137/158) reported at least one adverse event. • A total of 402 adverse events were recorded during the study: o 273 occurred during the treatment infusion period; o 162 were considered at least "possibly" related to treatment. • The adverse events most likely associated with one of the ketamine doses were agitation, anxiety, irritability, and constipation (i.e., these were infrequently reported in the standard and low dose ketamine groups; and were not reported in the placebo group). • Headache was more common in the low dose ketamine group. • Nightmare occurrence, and nausea (or other gastrointestinal disturbance), was comparable across groups.

9. Ketamine for Posttraumatic Stress Disorder: Standalone Intervention

Citation	Feder et al. (2021)
Study Design	• Double-blind, randomised, active-controlled, trial.
Sample Size	• 30 participants.
Population	• USA. • PTSD (chronic) and comorbid depression (DSM-5 criteria). • I (ketamine): 39.3 years (13.8); 13.3% male. • C (midazolam): 38.5 years (13.0); 33.3% male.
Intervention/s (I) and Comparator/s (C)	• All participants received six (40-minute) IV infusions (approximately three times per week for two consecutive weeks). • I (n = 15): ketamine (0.5 mg/kg). • C (n =15): midazolam (0.045 mg/kg).
Outcome Measure/s	• Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). • Montgomery-Asberg Depression Rating Scale (MADRS). • Clinical Global Impressions Severity (CGI-S) scale. • Clinical Global Impressions Improvement (CGI-I) scale. • Impact of Event Scale – Revised (IES-R).

Citation	Feder et al. (2021)
General	• Treatment response was defined as PTSD symptom improvement of at least (≥) 30% at week 3 (two weeks after the first IV infusion) as measured by the CAPS-5 (past-week version). • Treatment responders were followed weekly (for up to 4 weeks) then monthly (until loss of responder status), or for up to 6 months if there was no loss of responder status. • Mean PTSD duration for the full sample was 14.9 years (SD = 13.5). • Mean PTSD symptom levels were in the severe range at study enrolment. • Almost half the sample reported sexual assault or molestation as their primary or index trauma; followed by: physical assault or abuse; witnessing violent assault or death; having survived or responded to the 11 September 2001 terrorist attacks, and combat exposure. • Thirteen participants (43.3%) were on stable doses of concomitant psychotropic medications. • 17 participants (56.7%) were receiving concomitant psychotherapy. • Period study was conducted: June 2015 to January 2020.
Inclusion Criteria	• 18 to 70 years old. • Primary diagnosis of PTSD (chronic) as defined by: o DSM-5 criteria (at least 3 months' duration) determined by the Structured Clinical Interview for DSM-5 (SCID-5); and o Score of at least (≥) 30 on the CAPS-5 (past-week recall period): severe PTSD. • Stable on other psychotropic medications (e.g., antidepressants, antipsychotics, or mood stabilizers) for at least 3 months prior to study randomisation.
Exclusion Criteria	• Any serious, unstable medical condition. • Active suicidal or homicidal ideation (having a plan or unable to contract a no-harm agreement). • Lifetime history of psychotic or bipolar disorder, current anorexia or bulimia nervosa, alcohol or substance use disorder within 3 months of screening. • History of recreational ketamine or phencyclidine use on more than one occasion, or any use in the past 2 years. • Current treatment with a long-acting benzodiazepine or opioid medication.
Assessment Time-Point/s	• Baseline (prior to the first infusion). • Week 1 (prior to the fourth infusion). • Week 2 (after the sixth infusion).
Main Findings	• A significantly greater improvement in PTSD symptoms (as measured by the CAPS-5) was observed for the ketamine group compared with the midazolam group from baseline to week 2 [F (2, 55) = 5.97, p = 0.0045]. o While CAPS-5 scores were similar in both treatment groups at baseline (estimated difference = 0.87, SE = 3.93, p = 0.83), total CAPS-5 scores were significantly lower in the ketamine group at week 1 (estimated difference = 8.80, SE = 3.93, p = 0.030), and week 2 (estimated difference = 11.88, SE = 3.96, p = 0.004), compared with the midazolam group (effect size at week 1: d = 0.85, 95% CI = 0.10 to 1.59; at week 2: d = 1.13, 95% CI = 0.36 to 1.91). • A significantly greater improvement in depressive symptoms (as measured by the MADRS) was observed for the ketamine group compared with the midazolam group from baseline to week 2 [F (2, 55) = 5.68, p = 0.006, d = 0.92].

Citation	Feder et al. (2021)
	• A significantly greater improvement in global severity (as measured by the CGI-S) was observed for the ketamine group compared with the midazolam group from baseline to week 2 [F (2, 50) = 5.19, p = 0.009]. • A significant effect of treatment on global improvement (as measured by the CGI-I) was observed from week 1 to week 2 [F (1, 24) = 9.96, p = 0.004]. • There were no significant differences in symptom improvement from baseline to 24 hours after the first infusion on the total IES-R score [F (1, 28) = 0.08, p = 0.78], or past 24-hour MADRS score [F (1, 28) = 0.50, p = 0.48]. • The likelihood of a treatment response was significantly higher in the ketamine (67%; n = 10/15) group than in the midazolam (20%; n = 3/15) group (p = 0.03). • Among the ketamine responders, the median time to loss of treatment response was 27.5 days following the 2-week course of infusions. • In the subsample of 10 ketamine responders, the mean change from baseline to 24 hours was 226.0 on the total IES-R score (a 63.3% improvement on average), and 213.4 on the total past-24-hour MADRS score (a 53.3% improvement on average), which suggested that improvements in both PTSD and comorbid depressive symptoms were rapid when present. • When the integrity of the study blind was evaluated, the percentage of participants who correctly guessed their allocation to study condition did not significantly differ for the ketamine (46.7%; n = 7/15) compared with midazolam (35.7%; n = 5/14) group throughout the course of the study ($\chi 2$ = 4.89, p = 0.55).
Safety and Adverse Events	• Ketamine infusions were well tolerated overall. • No serious adverse events were reported. • After the start of infusions, the most frequently reported general side effects of ketamine (compared with midazolam) included: blurred vision (53% compared with 0%), dizziness (33% compared with 13%), fatigue (33% compared with 87%), headache (27% compared with 13%), and nausea or vomiting (20% compared with 7%).

10. Ketamine for Posttraumatic Stress Disorder: Standalone Intervention

Citation	Dadabayev et al. (2020)
Study Design	• Double-blind, randomised, active-controlled, trial.
Sample Size	• 39 participants (per-protocol sample). • 41 participants were randomised. • 2 participants withdrew from the CP + PTSD group. o 1 participant due to an unrelated medical emergency. o 1 participant was lost to follow-up.
Population	• USA. • Comorbid PTSD (DSM-5 criteria) and Chronic Pain (CP + PTSD) and Chronic Pain (CP). • I (ketamine: CP + PTSD): M = 45.3 years (SD = 11.18); 63.63% male. • I (ketamine: CP): M = 43.5 years (SD = 9.65); 90.0% male. • C (ketorolac: CP + PTSD): M = 40.1 years (SD = 9.73); 60.0% male. • C (ketorolac: CP): M = 52.9 years (SD = 8.61); 90.0% male.
Intervention/s (I) and Comparator/s (C)	• All participants received one (40-minute) IV infusion. • I (n = 21): ketamine (0.5 mg/kg). o Two diagnostic groups: CP + PTSD (n = 11); CP (n = 10). • C (n = 20): ketorolac (15 mg).

Citation	Dadabayev et al. (2020)
	○ Two diagnostic groups: CP + PTSD (n = 10); CP (n = 10).
Outcome Measure/s	• Impact of Event Scale – Revised (IES-R). • Visual Analogue Scale – Pain (VAS-P). • Brief Pain Inventory (BPI) – Short Form.
General	• Period study was conducted: January 2018 to June 2019.
Inclusion Criteria	• 18 to 65 years old. • Chronic Pain (CP) diagnosis as defined by the International Association for the Study of Pain (IASP); with symptoms persisting for at least 6 months. • PTSD diagnosis (DSM-5 criteria) as defined by the Clinician-Administered PTSD Scale-5 (CAPS-5); with symptoms persisting for at least 3 months. • All participants taking psychotropic and/or pain medications were required to be on stable doses for at least 6 weeks prior to study enrolment for the duration of the study.
Exclusion Criteria	• Non-English speaking. • Unwilling or unable to provide written informed consent. • Moderate-to-severe cognitive impairment as defined by a score of less than (<) 20 on the Mini-Mental State Examination (MMSE); administered by a trained clinician. • Current or lifetime history of psychotic or bipolar disorder. • Current bulimia or anorexia nervosa. • Active suicidal or homicidal ideation on presentation. • Active substance use disorder, or alcohol abuse or dependence in the previous 3 months. • Serious unstable medical illness or sleep apnoea. • HTN, prolonged QT interval, peptic ulcer disease, recent history of GI bleed, or renal insufficiency. • Pregnancy (confirmed by baseline lab test), the initiation of female hormonal treatments within 3 months of screening, or inability or unwillingness to use a medically accepted contraceptive method for the duration of the study.
Assessment Time-Point/s	• Pre-infusion. • Post-infusion: minute 15, 40, 120, 240; day 1, 2, and 7.
Main Findings	• PTSD symptoms (as measured by the IES-R) in the CP + PTSD groups: ○ PTSD symptoms decreased significantly from baseline to day 7 for both the ketamine and ketorolac treatments [$F(1,52) = 9.35$, $p < 0.01$]. ○ There was no significant effect of medication type, or differential effect of medication type from the pre- to post-infusion time points (both p's > 0.05). ○ Follow up analyses revealed significant decreases in PTSD symptom scores from baseline to day 1 [$t(32.59) = 2.33$, $p = 0.03$], and from baseline to day 7 [$t(27.53) = 2.93$, $p < 0.01$], but not from day 1 to day 7 [$t(31.75) = 0.92$, $p = 0.37$]. • PTSD symptoms (as measured by the IES-R) in the CP groups: ○ In the CP groups, PTSD symptoms did not significantly differ over time (pre- to post-infusion time points), or by medication type (ketamine vs. ketorolac), and there were no differential effects of medication type from the pre- to post-infusion time points (all p's > 0.05). • Pain symptoms (as measured by the VAS-P) in CP + PTSD and CP groups: ○ There was a significant effect of diagnostic group on pain symptoms over time ($p < 0.01$). ○ While both groups had improved pain scores on day 7; post-hoc analyses revealed that the improvement in pain symptoms was significantly greater

Citation	Dadabayev et al. (2020)
	in the CP + PTSD (M = -30.61, SD = 17.71) group compared with the CP (M = -14.28, SD = 15.87) group ($p < 0.001$).
Safety and Adverse Events	• In the CP group, both the ketamine and ketorolac infusions led to a significant increase in dissociative symptoms. • Unexpectedly, the ketamine and ketorolac infusions had less effect on dissociative symptoms in the CP + PTSD group.

11. Ketamine for Posttraumatic Stress Disorder: Combined Intervention (Psychotherapy)

Citation	Pradhan et al. (2017)
Study Design	• Randomised, controlled, trial. • Modified crossover design.
Sample Size	• 10 participants.
Population	• USA. • PTSD (DSM-IV criteria). • Treatment refractory. • Total sample: M = 43 years (SD = 13.3); 30% male.
Intervention/s (I) and Comparator/s (C)	• All participants received 12 sessions of individually tailored, mindfulness-based, trauma-focused psychotherapy (TIMBER): 3 sessions in the first week followed by 9 sessions conducted on a weekly basis. • All participants received a single IV infusion. • Using a modified crossover design, participants in the placebo group were switched to ketamine after they experienced a sustained relapse of PTSD. • I (n = 5) [TIMBER-K]: ketamine (0.5 mg/kg). • C (n = 5) [TIMBER-P]: placebo (saline).
Outcome Measure/s	• PTSD Checklist – Civilian Version (PCL-C). • CAPS (DSM-IV). • Hamilton Depression Rating Scale (HAM-D). • Beck Anxiety Inventory (BAI). • Assessment Scale for Mindfulness Interventions (ASMI).
General	• All participants were treatment refractory (for at least 6 months) before study recruitment and had been trialled (for at least 6 months) on treatment-as-usual (i.e., CBT and a therapeutic dose of at least two antidepressants: selective serotonin reuptake inhibitors, SSRIs; and selective norepinephrine reuptake inhibitors, SNRIs). • Participant trauma history: repeated sexual trauma (7 participants), motor vehicle accident (2 participants), and combat-related trauma (1 participant). • Mindfulness-based, trauma-focused psychotherapy (Trauma Interventions using Mindfulness Based Extinction and Reconsolidation for memories, TIMBER): the mindfulness interventions were personalised based on participant's scores on the Assessment Scale for Mindfulness Interventions (ASMI), which was administered at baseline, after 5 sessions, and after 9 sessions (completion). • Period study was conducted: not reported.
Inclusion Criteria	• Not reported.
Exclusion Criteria	• Not reported.

Citation	Pradhan et al. (2017)
Assessment Time-Point/s	• Ketamine. o Baseline. o 8 hours post-infusion. • Mindfulness. o Baseline. o During treatment: after 5 sessions of TIMBER. o End of treatment: after 9 sessions of TIMBER (completion). • Both. o Follow-up: 18 months post-infusion.
Main Findings	• For the nine participants who responded to treatment; significant differences were observed for: o PCL-C scores between baseline [M = 75.11 ± 8.28] and 4 hours [M = 45.67 ± 19.55] post-infusion (p = 0.003). o PCL-C scores between baseline [M = 75.11 ± 8.28] and 24 hours [M = 25.89 ± 6.01] post-infusion (p < 0.001). o CAPS scores between baseline [M = 87.56 ± 8.08] and 24 hours [M = 20.00 ± 7.73] post-infusion (p < 0.001). o HAM-D scores between baseline [M = 26.11 ± 5.9] and 24 hours [M = 4.33 ± 2.55] post-infusion (p < 0.001). o BAI scores between baseline [M = 48.89 ± 12.49] and 5 hours [M = 27.67 ± 15.31] post-infusion (p < 0.005). o BAI scores between baseline [M = 48.89 ± 12.49] and 24 hours [M = 8.56 ± 4.67] post-infusion (p < 0.001). • There was no significant difference in duration of treatment response for the TIMBER-K [M = 33 ± 22.98 days] and the TIMBER-P [M = 25 ± 16.8 days] group (p = 0.545). • A significantly longer treatment response was observed when participants crossed over from the TIMBER-P (control) group to the TIMBER-K (intervention) group [25 days vs. 49 days; p = 0.028).
Safety and Adverse Events	• No clinically significant side effects were observed (including cognitive side effects). • Two participants experienced mild nausea within the first hour post-infusion, which resolved without requiring medical intervention. • During the 18-month follow-up (outpatient department), no participants exhibited suicidal behaviour, required psychiatric hospitalisation, or dropped out of the study.

12. MDMA for Posttraumatic Stress Disorder: Combined intervention (Psychotherapy)

Citation	Mitchell et al. (2021)
Study Design	• Double-blind, randomised, placebo-controlled, trial. • Phase 3. • Multi-site.
Sample Size	• 91 participants. • One participant withdrew consent before dosing.
Population	• Fifteen study sites: 11 sites in USA (n = 77); 2 sites in Canada (n = 9); 2 sites in Israel (n = 5). • Severe PTSD (DSM-5 criteria). • Total sample: M = 41.0 years (SD = 11.9); 34.4% male. • MDMA: M = 43.5 years (SD = 12.9); 41.3% male.

Citation	Mitchell et al. (2021)
	• Placebo: M = 38.2 years (SD = 10.4); 27.3% male.
Intervention/s (I) and Comparator/s (C)	• 15 manualised therapy sessions (three preparatory + 3 MDMA-assisted + nine integrative). • I (n = 46): Single divided dose of MDMA (80-180mg). • C (n = 44): Single divided dose of placebo (80-180mg).
Outcome Measure/s	• Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). • Sheehan Disability Scale (SDS).
General	• The initial MDMA dose of 80mg was followed by a supplemental half-dose of 40mg (1.5 to 2.5 hours after the first dose). • In the second and third therapy sessions, an initial dose of 120mg was followed by a supplemental half-dose of 60mg. • Six participants in the MDMA group, and 13 participants in the placebo group, had PTSD (dissociative subtype) based on the CAPS-5 score. • Period study was conducted: 7 November 2018 to 26 May 2020.
Inclusion Criteria	• 18 years of age and over. • Fluent in speaking and reading the predominantly used or recognised language of the study site. • Able to swallow pills. • Agree to have all study visits recorded and provision of contact details in the event of a participant becoming suicidal or unreachable. • Must agree to inform the investigators within 48 hours of any medical conditions and procedures. • Negative pregnancy test at study entry, and prior to each experimental session, and must agree to use two adequate forms of birth control through 10 days after the last experimental session. • Lifestyle modifications: comply with requirements for fasting and refraining from certain medications prior to experimental sessions; not participate in any other interventional clinical trials during the duration of the study; remain overnight at the study site after each experimental session and be driven home after; and commit to medication dosing, therapy, and study procedures. • Diagnosis of PTSD (DSM-5 criteria) with a symptom duration of 6 months or longer. • May have well-controlled hypertension, that has been successfully treated with antihypertensive medicines, if they pass additional screening to rule out underlying cardiovascular disease. • May have asymptomatic Hepatitis C Virus (HCV) that has previously undergone evaluation and treatment as needed. • May have a history of, or current, Diabetes Mellitus (Type 2) if additional screening measures rule out underlying cardiovascular disease, if the condition is judged to be stable on effective management, and with the approval of the Medical Monitor. • May have hypothyroidism if taking adequate and stable thyroid replacement medication. • May have a history of, or current, glaucoma if approval for study participation is received from an ophthalmologist.
Exclusion Criteria	• Unable to give adequate informed consent. • Current problem which, in the opinion of the investigator or Medical Monitor, might interfere with participation. • Weight less than 48 kilograms. • Pregnant or nursing, or of childbearing potential and not practicing an effective means of birth control.

Citation	Mitchell et al. (2021)
Assessment Time-Point/s	• Baseline (T1). • After integrative therapy sessions: after session 1 (T2), after session 2 (T3), and after session 3 (T4).
Main Findings	• From baseline to 18 weeks, in the participants who completed treatment: o MDMA-assisted therapy was observed to significantly reduce PTSD symptoms (as measured by the CAPS-5) compared with placebo-assisted therapy ($p < 0.0001$; $d = 0.91$): the mean reduction in CAPS-5 scores was significantly larger in the MDMA-assisted therapy group [M(diff) = -24.4; SD = 11.6] than in the placebo-assisted therapy group [M(diff) = -13.9; SD = 11.5]. o MDMA-assisted therapy was observed to significantly reduce functional impairment (as measured by the SDS) compared with placebo-assisted therapy ($p = 0.0116$; $d = 0.43$): the mean reduction in SDS scores was significantly larger in the MDMA-assisted therapy group [M(diff) = -3.1; SD = 2.6] than in the placebo-assisted therapy group [M(diff) = -2.0; SD = 2.4].
Safety and Adverse Events	• Treatment-emergent adverse events, which were more prevalent in the MDMA study condition, were typically transient, mild to moderate in severity, and included muscle tightness, decreased appetite, nausea, hyperhidrosis, and feeling cold. • Although the number of participants who reported suicidal ideation varied throughout the visits, prevalence never exceeded baseline and was not exacerbated in the MDMA group. Serious suicidal ideation (C-SSRS score of 4 or 5) was minimal during the study and occurred almost entirely in the placebo arm.

13. MDMA for Posttraumatic Stress Disorder: Combined intervention (Psychotherapy)

Citation	Mithoefer et al. (2018)
Study Design	• Double-blind, dose-response, randomised, active-controlled, trial. • Phase 2. • Open-label crossover.
Sample Size	• 26 participants.
Population	• USA • PTSD (DSM-IV criteria). • Military veterans and first responders (firefighters or police officers). • Total sample: M = 37.2 years (SD = 10.3); 73% male. • Full-dose MDMA (125mg) group: M = 40.7 years (SD = 11.1); 67% male. • Part-dose MDMA (75mg) group: M = 29.1 years (SD = 4.0); 86% male. • Active-control MDMA (30mg) group: M = 39.2 years (SD = 9.7); 71% male.
Intervention/s (I) and Comparator/s (C)	• All participants received two 8-hour manualised psychotherapy sessions at approximately monthly intervals (i.e., 3 to 5 weeks apart). • I-1 (n = 12): full-dose MDMA (125mg). • I-2 (n = 7): part-dose MDMA (75mg). • C (n = 7): active-control MDMA (30mg).
Outcome Measure/s	• Primary. o Clinician Administered PTSD Scale for DSM-IV (CAPS). • Secondary. o Beck Depression Inventory – Second Edition (BDI-II). o Pittsburgh Sleep Quality Index (PSQI). o Post-Traumatic Growth Inventory (PTGI).

Citation	Mithoefer et al. (2018)
	○ Neuroticism Extroversion-Openness-Personality Inventory-Revised (NEO-PI-R). ○ Dissociative Experiences Scale II (DES-II). ○ Global Assessment of Functioning (GAF).
General	• MDMA was orally administered in each eight-hour therapy session; an optional supplementary dose of MDMA (half the initial dose) was administered 1.5 to 2 hours later. • Treatment response was defined as clinically significant decrease of ≥30% in the CAPS total score from baseline to 1 month after the second experimental session. • Period study was conducted: November 2010 to January 2015. • Secondary analyses in other papers. ○ Feduccia, Jerome, Mithoefer et al. (2021). ○ Gorman, Belser, Jerome et al. (2020). ○ Jerome, Feduccia, Wang et al. (2020). ○ Mithoefer, Feduccia, Jerome et al. (2019). ○ Ponte, Jerome, Hamilton et al. (2021).
Inclusion Criteria	• 18 years of age and over. • Military veterans, firefighters, or police officers. • Chronic PTSD resulting from traumatic experience during service. • PTSD duration of 6 months or more, and who had a total score ≥ 50 on the Clinician Administered PTSD Scale for DSM-IV (CAPS). • Failure to respond to, or inability to tolerate, previous pharmacotherapy or psychotherapy. • Required to taper and abstain from psychotropic medications during study participation except for sedative hypnotics or anxiolytics (used as required) between MDMA-assisted psychotherapy sessions. • Permitted comorbid disorders were anxiety disorders, affective disorders (except bipolar disorder type 1), substance abuse or dependence (in remission for ≥ 60 days) and eating disorders (without active purging).
Exclusion Criteria	• Major medical conditions except controlled hypertension or adequately treated hypothyroidism. • Pregnant or lactating women, or women not using effective contraception. • Additional exclusion criterion that cannot be revealed publicly until a future phase 3 trial is complete.
Assessment Time-Point/s	• Baseline. • Follow-up. ○ 1 month after the second experimental session (primary endpoint). ○ 12 months after the second experimental session.
Main Findings	• Significant decreases in PTSD symptoms (as measured by total score on the CAPS) were observed at the primary endpoint (one month after the second experimental session) for the full-dose (125mg) MDMA group [M(diff) = -44.3, SD = 28.7, p = 0.004] and part-dose (75mg) MDMA group [M(diff) = -58.3, SD = 9.8, p = 0.0005] compared with the active-control (30mg) MDMA group [M(diff) = -11.4, SD = 12.7]. • The part-dose (75mg) and full-dose (125mg) MDMA groups had significantly greater improvements in PTSD symptom severity than the active-control (30mg) MDMA group (p = 0.001); no significant differences were found between the part-dose (75mg) and full-dose (125mg) groups (p = 0.185). • Effect sizes were large for the part-dose (75mg) MDMA group (Cohen's d = 2.8; 95% CI = 1.19 to 4.39), and the full-dose (125 mg) MDMA group (Cohen's d =

Citation	Mithoefer et al. (2018)
	1.1; 95% CI = 0.04 to 2.08), compared with the active-control (30mg) MDMA group. • In the open-label crossover trial with full-dose (100 to 125mg) MDMA, PTSD symptoms significantly decreased in the group that had previously received active-control (30mg) MDMA (p = 0.01); however, no further significant decreases in PTSD symptoms were observed in the group that previously achieved a large treatment response after part-dose (75mg) MDMA in the blinded segment of the study (p = 0.81). • PTSD symptoms (as measured by total score on CAPS) were significantly reduced at the 12-month follow-up [M = 87.1, SD = 16.1] compared with baseline [M = 38.8, SD = 28.1] after all groups received full-dose MDMA (p < 0.0001).
Safety and Adverse Events	• 85 adverse events were reported by 20 participants. • Of these adverse events, four (5%) were serious: three were deemed unrelated, and one possibly related, to study drug treatment.

14. MDMA for Posttraumatic Stress Disorder: Combined intervention (Psychotherapy)

Citation	Ot'alora et al. (2018)
Study Design	• Double-blind, dose-response, randomised, active-controlled, trial. • Phase 2. • Open-label crossover.
Sample Size	• 28 participants.
Population	• USA. • Chronic PTSD (DSM-IV criteria). • Total sample: M = 42.0 years (SD = 12.9); 32.1% male. • 125mg MDMA: M = 44.6 years (SD = 15.4); 38.5% male. • 100mg MDMA: M = 39.6 years (SD = 9.8); 33.3% male. • 40mg (control) MDMA: M = 40.0 years (SD = 11.7); 16.7% male.
Intervention/s (I) and Comparator/s (C)	• All participants received two 8-hour manualised psychotherapy sessions spaced 1 month apart. • I-1 (n = 13): 125mg active-dose MDMA. • I-2 (n = 9): 100mg active-dose MDMA. • C (n = 6): 40mg comparator-dose MDMA.
Outcome Measure/s	• Clinician Administered PTSD Scale for DSM-IV (CAPS). • Beck Depression Inventory – Second Edition (BDI-II). • Dissociative Experiences Scale-II (DES-II). • Pittsburgh Sleep Quality Index (PSQI).
General	• Period study was conducted: October 2012 to February 2017. • Secondary analyses in other papers. o Feduccia, Jerome, Mithoefer et al. (2021). o Gorman, Belser, Jerome et al. (2020). o Jerome, Feduccia, Wang et al. (2020). o Mithoefer, Feduccia, Jerome et al. (2019).
Inclusion Criteria	• 18 years of age and over. • PTSD for at least (≥) six months, and a score of at least (≥) 50 on the Clinician Administered PTSD Scale for DSM-IV (CAPS). • Failure to respond to at least one course of pharmacotherapy and/or psychotherapy.

Citation	Ot'alora et al. (2018)
	• Physically healthy and free of psychiatric or medical contraindications for receiving MDMA
Exclusion Criteria	• Pregnant or lactating women.
Assessment Time-Point/s	• Baseline. • One month after the second blinded experimental session. • One month after the second open-label, active-dose session. • Two months after the third open-label, active-dose session. • Follow up: 12-months (± one month) after the final active-dose session.
Main Findings	• In the intention-to-treat set, the high-dose MDMA groups had the largest reduction in PTSD symptom severity (as measured by the CAPS) at the primary endpoint (baseline to one month after the second blinded session): 125mg dose [M(diff) = -26.3, SD = 29.5], 100mg dose [M(diff) = -24.4; SD = 24.2], and 40mg dose [M(diff) = -11.5, SD = 21.2]. However, there was no significant overall effect of treatment group (p = 0.52). Cohen's d effect sizes with 40mg MDMA group subtracted was 0.42 (-0.57, 1.42) for the 125mg MDMA group and 0.37 (-0.57, 1.42) for the 100mg MDMA group. • In the per-protocol set, a significant reduction in PTSD symptom severity (as measured by the CAPS) was observed [F (2,22) = 4.01, p = 0.03]: a significant reduction in PTSD symptoms was observed for the high-dose 125mg MDMA group [M = -37.0, SD = 20.9, p = 0.01], but not the high-dose 100mg MDMA group [M(diff) = -24.4, SD = 24.2, p = 0.10], compared to the low-dose 40mg MDMA group [M(diff) = -4.0, SD = 11.9]. Cohen's d effect sizes with 40mg MDMA group subtracted was 1.12 (-0.10, 2.35) for 125mg MDMA group and 0.73 (-0.45, 1.90) for 100mg MDMA group. • The per-protocol set included all participants who: (i) completed both blinded sessions; (ii) the primary outcome assessment; and (iii) did not experience a major protocol deviation. • At the 12-month follow-up, 76% (19/25) of the participants who completed treatment no longer met criteria for PTSD: for treatment completers, PTSD symptoms (as measured by CAPS) remained significantly lower than baseline (p < 0.001).
Safety and Adverse Events	• The treatment was well tolerated and there were no drug-related serious adverse events.

15. Psilocybin for Major Depressive Disorder: Combined intervention (Psychotherapy)

Citation	Davis et al. (2021)
Study Design	• Single-blind, randomised, waitlist-controlled, trial.
Sample Size	• 24 participants (per-protocol sample). • 27 participants randomised. • 3 participants withdrew: 2 in the immediate group; 1 in the delayed group.
Population	• USA. • Moderate or severe MDD episodes (DSM-5 criteria). • Total sample: M = 39.8 years (SD = 12.2); 33% male. • Immediate-treatment group: M = 43.6 years (SD = 13.0); 31% male. • Delayed-treatment group: M = 35.2 years (SD = 9.9); 36% male.
Intervention/s (I) and Comparator/s (C)	• All participants received at least 18 in-person visits over an 8-week period, including two day-long (approximately 11 hour) psilocybin dosing sessions.

Citation	Davis et al. (2021)
	• I (n = 13): immediate-treatment group (2 x doses psilocybin: 20mg/70 kg; 30mg/70 kg). • C (n = 11): delayed-treatment group (waitlist control).
Outcome Measure/s	• GRID-Hamilton Depression Rating Scale (GRID-HAMD). • Beck Depression Inventory – Second Edition (BDI-II). • Patient Health Questionnaire (PHQ). • Columbia Suicide Severity Rating Scale (C-SSRS). • Hamilton Anxiety Rating Scale (HAM-A). • State-Trait Anxiety Inventory (STAI).
General	• Period study was conducted: August 2017 to April 2019 (4-week primary outcome assessments were completed in July 2019).
Inclusion Criteria	• 21 to 75 years old. • No current pharmacotherapy for depression (self-reported), and willing/able to refrain from using antidepressants (e.g., selective serotonin reuptake inhibitors) for at least 5 half-lives before study screening and up to 4 months after study enrolment (through completion of the primary outcome assessment). • Medically stable with no uncontrolled cardiovascular conditions. • No personal or family history (first or second degree) of psychotic or bipolar disorders. • Not pregnant or breastfeeding, and using contraception.
Exclusion Criteria	• Individuals with a moderate or severe substance use disorder (including nicotine) in the past year (DSM-5 criteria). • Individuals with substantial lifetime use (> 10 total), or recent use (past 6 months), of ketamine or classic hallucinogens, such as psilocybin-containing mushrooms or lysergic acid diethylamide.
Assessment Time-Point/s	• Baseline. • Primary endpoint (between groups): week 5 and 8 (post-randomisation). • Primary endpoint (within groups): week 1 and 4 (post-session). • Follow-up visits (both groups): week 1 and 4 after the second psilocybin session.
Main Findings	• Depressive symptoms (as measured by the GRID-HAMD) were significantly lower at week 1 [M = 8.0, SD = 7.1] and week 4 [M = 8.5, SD = 5.7] in the immediate-treatment group than at comparable time-points in the delayed-treatment group: week 5 [M = 23.8, SD = 5.4] and week 8 [M = 23.5, SD = 6.0]. • The effect sizes were large at week 5 [Cohen's d = 2.5, 95% CI = 1.4 to 3.5, p < 0.001] and week 8 [Cohen's d = 2.6, 95% CI = 1.5 to 3.7, p < 0.001]. • A significant reduction in depressive symptoms (as measured by the QIDS-SR) was observed from baseline [M = 16.7, SD = 3.5] to day 1 [M = 6.3, SD = 4.4] following session 1 [Cohen's d = 2.6, 95% CI = 1.8 to 3.5, p < 0.001], which remained significantly reduced through week 4 [M = 6.0, SD = 5.7] following session 2 [Cohen's d = 2.3, 95% CI = 1.5 to 3.0, p < 0.001]. • In the overall sample: o 17 participants (71%) at week 1, and 17 participants (71%) at week 4 met criteria for a clinically significant treatment response (≥ 50% reduction in GRID-HAMD score); o 14 participants (58%) at week 1, and 13 participants (54%) at week 4, met criteria for remission (GRID-HAMD score ≤ 7).
Safety and Adverse Events	• No serious adverse events were reported. • One participant experienced a transient increase in blood pressure that exceeded the protocol criteria for more frequent assessment (i.e., diastolic

Citation	Davis et al. (2021)
	blood pressure > 100 mmHg) occurred twice during one session, but no medical intervention was needed, and the blood pressure level remained within predetermined safety parameters and resolved spontaneously during the session. • Other adverse events were reported by participants after completing at least one-half of the psilocybin sessions included challenging emotional (e.g., fear and sadness) and physical (e.g., feeling body shake or tremble) experiences. • Mild to moderate transient headache was reported during 16 of 48 sessions (33%) and after the subjective psilocybin effects had subsided after 14 of 48 sessions (29%).

16. Psilocybin for Major Depressive Disorder: Combined Intervention (Psychological Support)

Citation	Carhart-Harris et al. (2021)
Study Design	• Double-blind, phase 2, randomised, controlled, trial.
Sample Size	• 59 participants.
Population	• United Kingdom. • Long-standing, moderate-to-severe major depressive disorder (criteria not specified). • Total sample: M = 41 years (SD = not reported); 66% male.
Intervention/s (I) and Comparator/s (C)	• All participants received psychological support: two therapist 'guides' supported each participant in all visits and sessions via preparation sessions; use of pre-recorded music during psilocybin administration; and integration sessions. • I (n = 30): psilocybin group: two doses of psilocybin (25 mg), 3 weeks apart, plus 6 weeks of daily oral placebo. • C (n = 29): escitalopram group: Two doses of psilocybin (1 mg), 3 weeks apart, plus 6 weeks of daily oral Escitalopram (10 mg in the first 3 weeks and increased to 20 mg in the second 3 weeks).
Outcome Measure/s	• Primary. o Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR-16). • Secondary (not exhaustive). o Beck Depression Inventory – 1A (BDI-1A). o Hamilton Depression Rating Scale (HAM-D). o Montgomery-Asberg Depression Rating Scale (MADRS).
General	• Depression had been present for a mean of 22 years among the participants in the psilocybin group and for a mean of 15 years among those in the escitalopram group; however, there was more current alcohol use among the participants in the escitalopram group than in the psilocybin group. • Period study was conducted: January 2019 to March 2020.
Inclusion Criteria	• Score of at least 17 on Hamilton Depression Scale (HAM-D) indicating moderate-to-severe Major Depressive Disorder (MDD). • Confirmation of a diagnosis of depression from the participant's general physician.
Exclusion Criteria	• Personal (or immediate family) history of psychosis. • Medically significant health conditions that make a person unsuitable to participate in the trial (as assessed by a physician). • History of serious suicide attempts.

Citation	Carhart-Harris et al. (2021)
	• Positive pregnancy test. • Contraindications for Selective Serotonin Reuptake Inhibitors (SSRIs) or undergoing magnetic resonance imaging (MRI). • Previous use of escitalopram (although previous use of psilocybin was allowed). • Known (or suspected) pre-existing psychiatric condition (e.g., borderline personality disorder) that could jeopardize rapport between the patient and the two mental health caregivers within the trial.
Assessment Time-Point/s	• Baseline (7 to 10 days before visit 1). • Primary outcome/s (visit 6: 3 weeks after visit 5).
Main Findings	• No significant difference in the depressive symptoms (as measured by the QIDS-SR-16) were observed for the psilocybin group [M = -8.0, SE = ± 1.0] compared with the escitalopram group [M = -6.0, SE = ± 1.0] from baseline to week 6 (p = 0.17). • 70% of the participants in the psilocybin group, and 48% participants in the escitalopram group, met criteria for a treatment response: a between-group difference of 22 percentage points (95% CI = -3 to 48). • 57% of participants in the psilocybin group, and 28% of participants in the escitalopram group, met criteria for remission: a between-group difference of 28 percentage points (95% CI = 2 to 54). • However, there were no significant differences between the psilocybin group and the escitalopram group in terms of treatment response or remission. • Secondary outcomes generally favoured psilocybin over escitalopram, but the analyses were not corrected for multiple comparisons.
Safety and Adverse Events	• No serious adverse events were reported. • The percentage of participants reporting any adverse events was similar across groups: 87% (n = 26/30) in the psilocybin group and 83% (n = 24/29) in the escitalopram group. • The percentage of participants who had increased anxiety and dry mouth was higher in the escitalopram group than in the psilocybin group (14% vs. 0%). • Adverse events in the psilocybin group typically occurred within 24 hours of the dosing day; the most common adverse event was headache.

17. Ayahuasca for Social Anxiety Disorder: Standalone Intervention

Citation	Dos Santos et al. (2021)
Study Design	• Double-blind, randomised, placebo-controlled, trial. • Pilot, proof-of-concept.
Sample Size	• 17 participants. • Three participants were excluded from all analyses (except BAI data) due to equipment failure (2 in the ayahuasca group, 1 in the placebo group).
Population	• Brazil. • Social Anxiety Disorder (DSM-5 criteria). • Total sample: M = 24.9 years (range = 19 to 32 years); 11.8% male.
Intervention/s (I) and Comparator/s (C)	• All participants received an oral liquid. • I (n = 9): ayahuasca (2 mL/kg). • C (n = 8): placebo (2mL/kg).
Outcome Measure/s	• Visual Analog Mood Scale (VAMS) – Brazilian version. • Self-Statements during Public Speaking Scale (SSPS) – Brazilian version.

Citation	Dos Santos et al. (2021)
	• The Bodily Symptoms Scale (BSS). • Beck Anxiety Inventory (BAI) – Brazilian version.
General	• Period study was conducted: September 2015 to July 2019.
Inclusion Criteria	• 18 to 65 years old. • Score of at least (≥) 19 on the Social Phobia Inventory (SPIN), as a cut-off for Social Anxiety Disorder (SAD); or sub-clinical anxiety symptoms of excessive fear, anxiety, or avoidance in social situations (self-report). • Social anxiety disorder (SAD) diagnosis as assessed by the Structured Clinical Interview for DSM-5 – Clinician Version (SCID-5-CV). • No prior use of ayahuasca (self-report), and no more than (≤) 2 lifetime uses (self-report) of other hallucinogens (LSD, psilocybin, DMT, mescaline, other tryptamines, and phenethylamine).
Exclusion Criteria	• Current treatment for SAD (pharmacological and/or psychotherapeutic). • Current, or history of, cardiovascular, liver, or neurological diseases. • Any current psychiatric diagnosis (except for SAD and comorbid anxiety disorders). • Use of psychoactive medications (antidepressants, mood stabilisers, anxiolytics, and antipsychotics). • Recurrent use (more than 2 times/month) of drugs of abuse (cannabis and cocaine confirmed by urinalysis; other drugs by self-report). • Pregnant or lactating women.
Assessment Time-Point/s	• Study (11 time-points): baseline to minute 355. • Initial psychoactive phase (6 time-points): baseline and minute 40, 90, 120, 180, and 240. • Public-speaking task (5 time-points): minute 300 to 355. • Follow-up (3 time-points): day 7, 14, and 21.
Main Findings	• Significant improvements in (self-reported) self-perception of speech performance (as measured by the SSPS – Brazilian version) were observed for the ayahuasca group compared with the placebo group over the five time-points relevant to the public speaking test ($p = 0.017$; $n = 14$). • No significant between-group differences in self-reported anxiety symptoms (as measured by the BAI) over time ($p > 0.05$; $n = 17$). • While all 17 participants were included in the analysis of the BAI data; the ayahuasca and placebo groups were not comparable at baseline (i.e., ayahuasca: $M = 13.9$, $SD = 13.1$; placebo: $M = 5.0$, $SD = 4.2$).
Safety and Adverse Events	• Ayahuasca was generally well tolerated; mainly producing nausea, gastrointestinal discomfort, and vomiting. • During the peak effects of ayahuasca (1 to 1.5 hours after drug intake), one participant reported transient (20 to 30 minutes) confusion, fear, distress, and depersonalization/dissociation (i.e., anguish, fear of dying or going crazy, alterations in body perception, and lost track of time).

18. Ayahuasca for Major Depressive Disorder: Standalone Intervention

Citation	Palhano-Fontes et al. (2019)
Study Design	Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 29 participants (per-protocol sample). • 35 participants were randomised and 6 were excluded from analysis: 3 in the ayahuasca group; and 3 in the placebo group.

Citation	Palhano-Fontes et al. (2019)
Population	• Brazil. • Major Depressive Disorder (DSM-IV criteria). • Treatment resistant. • Ayahuasca group: M = 39.71 years (SD = ± 11.26); 21.43% male. • Placebo group: M = 44.2 years (SD = ± 11.98); 33.33% male.
Intervention/s (I) and Comparator/s (C)	• All participants received an oral liquid. • I (n = 14): Ayahuasca (1 mL/kg); adjusted to contain 0.36 mg/kg of N,N-DMT. • C (n = 15): Placebo (1 mL/kg).
Outcome Measure/s	• Hamilton Depression Rating Scale (HAM-D, primary outcome). • Montgomery-Asberg Depression Rating Scale (MADRS). • Clinician-Administered Dissociative States Scale (CADSS). • Brief Psychiatric Rating Scale (BPRS). • Young Mania Rating Scale (YMRS).
General	• On average, participants met criteria for moderate-to-severe depression: HAM-D (M = 21.83, SD = ± 5.35); MADRS (M = 33.03, SD = ± 6.49). • Participants had been experiencing depressive symptoms for many years (M = 11.03, SD = ± 9.70) and had unsuccessfully trialled multiple antidepressants (M = 3.86, SD = ± 1.66). • Two participants had a previous history of electroconvulsive therapy (ECT). • Most participants (76%) had a comorbid personality disorder; 31% had a comorbid anxiety disorder. • All participants regularly used benzodiazepines during the trial; benzodiazepines were allowed as a supporting hypnotic and/or anxiolytic agent. • Treatment response was defined as a reduction of at least (≥) 50% in either HAM-D or MADRS scores (relative to baseline). • Remission was defined as HAM-D score of no more than (≤) 7 or MADRS score of no more than (≤) 10. • Period study was conducted: January 2014 to June 2016.
Inclusion Criteria	• 18 to 60 years old. • Major Depressive Disorder (unipolar) as diagnosed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). • Treatment-resistant depression defined as an inadequate response to at least two classes of antidepressant medications. • Moderate-to-severe depressive episode (at screening) as defined by a score of at least (≥) 17 on the Hamilton Depression Rating Scale (HAM-D).
Exclusion Criteria	• Previous experience with ayahuasca. • Current medical disease based on history. • Pregnant. • Current or previous history of neurological disorders. • Personal or family history of schizophrenia or bipolar affective disorder, mania or hypomania, use of substances of abuse, and suicidal risk.
Assessment Time-Point/s	• Baseline. • Post-treatment: day 1, 2, and 7 (after dosing).
Main Findings	• Depressive symptoms (as measured by the HAM-D) o At day 7, a significant difference in depressive symptoms (as measured by the HAM-D) was observed for the ayahuasca group compared with the placebo group [F (1) = 6.31, p = 0.019, Cohen's d = 0.98, 95% CI = 0.21 to 1.75]. o At day 7, the rate of treatment response (as measured by the HAM-D) was significantly different between groups; with 57% of responders in the

Citation	Palhano-Fontes et al. (2019)
	ayahuasca group and 20% in the placebo group [OR = 5.33, 95% CI = 1.11 to 22.58, p = 0.04, NNT = 2.69]. o At day 7, the rate of remission (as measured by the HAM-D) did not significantly differ between groups; with 43% of remitters in the ayahuasca group compared with 13% in the placebo group [OR = 4.87, 95% CI = 0.77 to 26.73, p = 0.07, NNT = 3.39]. • Depressive symptoms (as measured by the MADRS) o Linear mixed model showed a significant effect for time [F (2, 34.4) = 3.96, p = 0.028), treatment [F (1, 27.7) = 10.52, p = 0.003], but no treatment by time interaction [F (2, 34.4) = 1.77; p = 0.185). o MADRS scores were significantly lower in the ayahuasca group compared with the placebo group at day 1 (p = 0.04), day 2 (p = 0.04), and day 7 (p < 0.0001). o Between-group effect sizes increased from day 1 to day 7 (day 1: Cohen's d = 0.84; day 2: Cohen's d = 0.84; day 7: Cohen's d = 1.49). o At day 1, the rate of treatment response (as measured by the MADRS) was high for both groups: 50% in the ayahuasca group, and 46% in the placebo group [OR = 1.17, 95% CI = 0.26 to 5.48, p = 0.87, NNT = 26]. At day 2, response rates remained high in both groups: 77% in the ayahuasca group and 64% in the placebo group [OR = 1.85, 95% CI = 0.29 to 8.40, p = 0.43, NNT = 7.91]. Response rate was statistically different at day 7: 64% of responders in the ayahuasca group, and 27% in the placebo group [OR = 4.95, 95% CI = 1.11 to 21.02, p = 0.04, NNT = 2.66]. o At day 1, the rate of remission rate (as measured by the MADRS) was 42% in the ayahuasca group and 46% in the placebo group (p = 0.86). At day 2, the remission rate was 31% in the ayahuasca group and 50% in the placebo group (p = 0.31). At day 7, the remission rate was 36% in the ayahuasca group and 7% in the placebo group [OR = 7.78, 95% CI = 0.81 to 77.48, p = 0.054, NNT = 3.44].
Safety and Adverse Events	• No serious adverse events were observed during or after dosing. • Observations included: transient nausea (ayahuasca = 71%, placebo = 26%; p = 0.027); vomiting (ayahuasca = 57%, placebo = 0%; p = 0.0007), transient anxiety (ayahuasca = 50%, placebo = 73%; p = 0.263), restlessness (ayahuasca = 50%, placebo = 20%; p = 0.128), and transient headache (ayahuasca = 42%, placebo = 53%; p = 0.715). • Some participants reported the ayahuasca experience was accompanied by a high level of psychological distress. • Most participants were discharged home accompanied by a friend or relative at the end of the 8-hour dosing session. • Four participants who presented in a delicate condition following dosing remained as inpatients on the hospital ward for a week.

Appendix 8: Risk of Bias Assessments (RoB 2)

Psychedelic compounds: Standalone and combined interventions (n = 18)

#	Study	Intervention	Comparator	D1	DS	D2	D3	D4	D5		Overall	n
1	Taylor et al. (2018)	Ketamine	Placebo	+	x	--	+	+	--		x	18
2	Daly et al. (2021)	Ketamine	Placebo	+		--	x	x	+		x	223
3	Dakwar et al. (2018)	Ketamine	Midazolam	+	+	x	+	+	x		x	18
4	Dakwar et al. (2017)	Ketamine	Midazolam	+	+	x	--	+	--		x	20
5	Dakwar et al. (2019)	Ketamine	Midazolam	--		--	x	+	+		x	55
6	Dakwar et al. (2020)	Ketamine	Midazolam	--		--	+	+			x	40
7	Grabski et al. (2020)	Ketamine	Placebo	+		--	--	+	+		--	96
8	Abdallah et al. (2022)	Ketamine	Placebo	+		+	+	+	+		+	158
9	Feder et al. (2021)	Ketamine	Midazolam	+		+	+	+	--		--	30
10	Dadabayev et al. (2020)	Ketamine	Ketorolac	--		--	+	+	--		--	39
11	Pradhan et al. (2017)	Ketamine	Placebo	x	+	x	+	+	--		x	10
12	Mitchell et al. (2021)	MDMA	Placebo	+		+	+	--	+		--	91
13	Mithoefer et al. (2018)	MDMA (high doses)	MDMA (low dose)	+		+	+	--	+		--	26
14	Ot'alora et al. (2018)	MDMA (high doses)	MDMA (low dose)	+		+	+	--	+		--	28
15	Davis et al. (2021)	Psilocybin	Waitlist	+		--	+	x	+		x	24
16	Carhart-Harris et al. (2021)	Psilocybin	Escitalopram	+		+	+	+	+		+	59
17	Dos Santos et al. (2021)	Ayahuasca	Placebo	x		--	--	x	x		x	17
18	Palhano-Fontes et al. (2019)	Ayahuasca	Placebo	--		--	--	+	--		x	29

Notes. n = sample size. D1 = Bias arising from the randomisation process. DS = Bias arising from period and carryover effects. D2 = Bias due to deviations from the intended interventions. D3 = Bias due to missing outcome data. D4 = Bias in measurement of the outcome. D5 = Bias in selection of the reported result.

Risk of Bias Judgments	Symbol
Low risk	+
Some concerns	--
High risk	x

Appendix 9: GRADE Certainty of Evidence Summaries

Psychedelic compounds: Standalone and combined interventions (n = 18)

Intervention (no. of studies)	Design (no. of studies)	RoB Assessments (no. of studies)	Precision and Consistency	Directness	Publication Bias	GRADE Summary[1,2]
Ketamine (11)	Parallel arm RCT (7) Crossover RCT (4)	Serious (7 high risk; 3 some concerns; 1 low risk)	Serious	Not serious	Not suspected	Low ⨁⨁
MDMA (3)	Parallel arm RCT (3)	Not serious, borderline (0 high risk; 3 some concerns; 0 low risk)	Not serious, borderline	Not serious	Not suspected	Moderate ⨁⨁⨁
Psilocybin (2)	Parallel arm RCT (2)	Not serious, borderline (1 high risk; 0 some concerns; 1 low risk)	Serious	Not serious	Not suspected	Low ⨁
Ayahuasca (2)	Parallel arm RCT (2)	Serious (2 high risk; 0 some concerns; 0 low risk)	Serious	Serious	Not suspected	Very Low ⨁
LSD (0)	X	X	X	X	X	X

Notes. LSD = Lysergic acid diethylamide. MDMA = Methylenedioxymethamphetamine. RCT = randomised controlled trial. RoB = risk of bias. 1. GRADE summary includes the risk of bias assessments, precision of the effect estimates, consistency of the individual study results, how directly the evidence answers the question of interest, and risk of publication or reporting biases (NHMRC, 2019). 2. Commonly used symbols to describe the certainty of evidence in evidence profiles: High ⨁⨁⨁⨁, Moderate ⨁⨁⨁, Low ⨁⨁, and Very Low ⨁.

The interpretation of the four levels of evidence used in the evidence summaries are as follows:

GRADE	Definition
High ⨁⨁⨁⨁	High confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect.
Moderate ⨁⨁⨁	Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⨁⨁	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very Low ⨁	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

1. GRADE rating of ketamine studies

GRADE domain	Judgement	Concerns about certainty domains
Study limitations (risk of bias)	All 11 studies were randomised controlled trials; four studies employed a crossover design. Only one study was judged to have a low risk of bias (Abdallah et al., 2022). Three of the 11 studies (Feder et al., 2021; Grabski et al., 2020; Dadabayev et al., 2020) had some risk-of-bias concerns. The remaining seven studies had a high risk of bias: three studies (Pradhan et al., 2017, Dakwar et al., 2018, Dakwar et al., 2017) inappropriately used per-protocol analysis (rather than intention-to-treat analysis); three studies (Dakwar et al., 2020; Dakwar et al., 2019; Daly et al., 2021) had issues with missing outcome data, outcome measurement, and/or selective outcome reporting; and one study (Taylor et al. 2018) had evidence of significant carryover effects on the primary outcome measure (crossover design). Therefore, the evidence was judged to have serious methodological limitations.	Serious
Precision and Consistency	The total number of participants included in the 11 studies was 707. Five studies had small sample sizes of 30 participants or less. One study (Daly et al., 2021: *n* = 223) reported significant effects for treatment-resistant depression with/without comorbid anxiety (anxiety outcomes not reported; note also the established literature on ketamine for depression). One study (Taylor et al., 2018; *n* = 18) reported a significant reduction in social anxiety symptoms for the clinician-administered outcome measure, but not the self-reported outcome measure. Three studies (Dakwar et al., 2018; Dakwar et al., 2017; Dakwar et al., 2019) reported significant effects for cocaine use disorder. However, two of the three studies had small numbers of participants (*n* = 18 and *n* = 20, respectively). In the third study (Dakwar et al., 2019; *n* = 55), over 40% of participants (*n* = 23) discontinued or were lost to follow-up (unbalanced across groups: 16 in the ketamine group; 7 in the midazolam group). Two studies (Dakwar et al., 2020; Grabski et al., 2022) reported mixed or non-significant effects for alcohol use disorder; with the non-significant effects observed in the larger of the two studies (Grabski et al., *n* = 96) that had a lower risk of bias. Four studies (Abdallah et al., 2022; Feder et al., 2021; Dadabayev et al., 2020; Pradhan et al., 2017) reported mixed effects for PTSD. The largest study (Abdallah et al., 2022) contributed two-thirds (*n* = 158) of the participants with PTSD (*n* = 237) and reported non-significant effects. Therefore, the evidence was judged to have serious imprecision and inconsistency.	Serious
Directness	Ten of the 11 studies examined IV ketamine infusions; one study examined esketamine nasal spray. Five of the 11 studies used a combined intervention where a psychedelic intervention was used in conjunction with either a pharmacological intervention (i.e.,	Not serious

GRADE domain	Judgement	Concerns about certainty domains
	antidepressant medication: Daly et al., 2021) or a psychotherapeutic intervention (i.e., psychedelic-assisted psychotherapy: Dakwar et al., 2019; Dakwar et al., 2020; Grabski et al., 2022; Pradhan et al., 2017). The studies that employed a standalone intervention usually allowed participants to remain on stable treatment regimens (pharmacotherapy and/or psychotherapy), or recruited participants with substance use disorders without psychiatric comorbidities. One study focused on social anxiety disorder; one study focused on treatment-resistant depression with/without comorbid anxiety; five studies focused on substance use disorders (three: cocaine use; two: alcohol use); and four studies focused on PTSD. Therefore, the studies were judged to provide direct evidence on the review question.	
Publication bias	Publication bias was not suspected as the studies reported a mix of positive and negative findings, and the search for studies was comprehensive.	Not suspected

2. GRADE rating of MDMA studies

GRADE domain	Judgement	Concerns about certainty domains
Study limitations (risk of bias)	All three studies of MDMA-assisted therapy were judged to have some risk-of-bias concerns. Two studies (Mithoefer et al., 2018; Ot'alora et al., 2018) used low dose MDMA as an active control. In both studies, therapists correctly guessed treatment allocation most of the time. There was reportedly some success in participant blinding for the Mithoefer et al. (2018) study. Mitchell et al. (2021) did not formally assess the efficacy of the study blind; however, at the time of unblinding, participants correctly guessed their allocation to study condition almost 100% of the time. Therefore, the evidence was judged to have borderline methodological limitations.	Not serious, borderline
Precision and Consistency	The total number of participants included in the studies was 136. Mitchell et al. (2021; *n* = 82) contributed the majority share (60%) and reported significant treatment effects. Ot'alora et al. (2018; *n* = 28) did not report significant treatment effects in an intention-to-treat analysis. Mithoefer et al. (2018; *n* = 26) demonstrated a much larger treatment effect (Cohen's d = 2.8; 95% CI = 1.19 - 4.39) for the 75mg MDMA group compared with the 125mg MDMA group (Cohen's *d* = 1.1; 95% CI = 0.04 - 2.08). The large confidence interval for the latter group is almost inclusive of no effect, possibly due to the small sample size. Therefore, the evidence was judged to have borderline imprecision and inconsistency.	Not serious, borderline

GRADE domain	Judgement	Concerns about certainty domains
Directness	All three studies recruited participants with PTSD and included psychotherapy for all participants. Therefore, the studies were judged to provide direct evidence on the review question.	Not serious
Publication bias	Publication bias was not suspected as the studies reported a mix of positive and negative findings, and the search for studies was comprehensive.	Not suspected

3. GRADE rating of psilocybin studies

GRADE domain	Judgement	Concerns about certainty domains
Study limitations (risk of bias)	One of the two studies (Davis et al., 2021) was judged to have a high risk of bias due to concerns with outcome measurement. Participants in the delayed-treatment group (8-week waitlist control) were monitored via weekly telephone calls or in-person visits to assess depressive symptoms and suicide risk. Participants were likely aware of the treatment allocations, which may have influenced the self-reported outcome measures. Finally, the study employed per-protocol analysis (rather than intention-to-treat analysis). The Carhart-Harris et al. (2021) study contributed a larger proportion of participants to the overall sample size and was judged to have a low risk of bias. Thus, the studies were judged to have borderline methodological limitations.	Not serious, borderline
Precision and Consistency	The total number of participants included in the studies was 83. The Carhart-Harris et al. (2021; *n* = 59) study contributed the majority (71%) of participants, and reported non-significant effects (with wide confidence intervals despite the larger participant sample). The Davis et al. (2021; *n* = 24) reported large effect sizes that were undermined by the study's methodological limitations. Therefore, the studies were judged to have serious imprecision and inconsistency.	Serious
Directness	Both studies recruited participants with a major depressive disorder and included supportive psychotherapy for all participants. Therefore, the studies were judged to provide direct evidence on the review question.	Not serious
Publication bias	Publication bias was not suspected as the studies reported a mix of positive and negative findings, and the search for studies was comprehensive.	Not suspected

4. GRADE rating of ayahuasca studies

GRADE domain	Judgement	Concerns about certainty domains
Study limitations (risk of bias)	Both studies were judged to have high risk of bias. In the Dos Santos et al. (2021) study, the study blind failed (i.e., both the participants and researchers correctly guessed the allocation to study conditions 100% of the time). Additionally, three participants were excluded from all analyses (except the BAI data) due to equipment failure (two in ayahuasca group; one in the placebo group). Finally, while all 17 participants were included in the analysis of the BAI data; the ayahuasca and placebo groups were not comparable at baseline. The Palhano-Fontes et al. (2019) study employed per-protocol analysis (rather than intention-to-treat analysis), excluding six participants following randomisation. There is a potential imbalance in baseline characteristics between groups, with participants in the placebo group older and having lower HAM-D and MADRS scores than those in ayahuasca group. Additionally, no pre-specified statistical analysis plan was available. Thus, the planned outcome measures and analyses could not be compared with those reported in the published article. Therefore, the studies were judged to have serious methodological limitations.	Serious
Precision and Consistency	The total number of participants included in the trials was 46, with the majority (71%) of participants contributed by the Palhano-Fontes et al. (2019; *n* = 29) study. The Dos Santos et al. (2021) study reported a significant effect of ayahuasca on self-reported public speaking performance (SSPS), but no effect on self-reported anxiety (BAI). Palhano-Fontes et al. (2019) reported a significant effect of ayahuasca on depressive symptoms, and rates of treatment response, but not rates of remission (as measured by both the HAM-D and the MADRS). Therefore, studies were judged to have serious imprecision and inconsistency.	Serious
Directness	The Dos Santos et al. (2021) study recruited (predominantly female) undergraduate students with social anxiety disorder. The Palhano-Fontes et al. (2019) study recruited (predominantly female) participants with high rates (76%) of comorbid personality disorder. Therefore, the studies were considered to have serious indirectness in relation to the review question.	Serious
Publication bias	Publication bias was not suspected as the studies reported a mix of positive and negative findings, and the search for studies was comprehensive.	Not suspected

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