Evidence Compass

Technical Report

Hallucinogens as treatments for PTSD,

anxiety, and depression:

A Rapid Evidence Assessment

November 2017

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Glossary of Terms

Term	Definition
5-HT	5-hydroxytryptamine
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	Brain-derived neurotrophic factor
CAPS	Clinician-administered PTSD scale
CB1	Cannabinoid receptor type 1
CB2	Cannabinoid receptor type 2
CBT	Cognitive behavioural therapy
DMN	Default mode network
DVA	Department of Veterans' Affairs
eCB	Endocannabinoid system
ECT	Electroconvulsive therapy
GHB	Gamma-hydroxybutyric acid
HPPD	Hallucinogen persisting perception disorder
LSD	Lysergic acid diethylamide
MDD	Major depressive disorder
MDMA	3,4-methylenedioxymethamphetamine
mRNA	Messenger ribonucleic acid
NMDA	N-methyl-D-aspartate
OCD	Obsessive-compulsive disorder
PF	Pre-frontal
PICO	Patient, problem or population; Intervention; Comparison, control, or comparator; Outcome
PTSD	Posttraumatic stress disorder
RCT	Randomised controlled trial
REA	Rapid evidence assessment
REM	Rapid eye movement
SSRI	Selective serotonin reuptake inhibitor
THC	Tetrahydrocannabinol
vmPFC	Ventromedial prefrontal cortex

Executive Summary

- The aim of this rapid evidence assessment (REA) was to assess the evidence related to hallucinogenic drug interventions for PTSD, anxiety, and depression in adults.

- Literature searches were conducted to identify studies that investigated the efficacy of hallucinogens for treating PTSD, anxiety, and depression. Studies were excluded if the full text was unavailable, if the drug was not investigated as a treatment, if the paper was not peer-reviewed, if the primary outcome measures were not the focus of the review (i.e., PTSD, anxiety and depression), if they did not concern the population of interest (i.e., adults), and in the case of ketamine only, if the drug (i.e., ketamine) was used as an adjunctive therapy. Given that there was a large amount of literature found for ketamine, only randomised controlled trials, or systematic reviews and meta-analyses were examined for ketamine. Therefore, ketamine studies which were not these designs were excluded. Studies were assessed for quality of methodology, risk of bias, and quantity of evidence, and the consistency, generalisability, and applicability of the findings to the population of interest. These assessments were then collated for each drug type to determine an overall ranking of level of support for each type of drug for the treatment of PTSD, anxiety, and depression.

- The ranking categories were: 'Supported' – clear, consistent evidence of beneficial effect; 'Promising' – evidence suggestive of beneficial effect but further research required; 'Unknown' – insufficient evidence of beneficial effect; 'Not supported' – clear, consistent evidence of no effect or negative/harmful effect.

- Twenty-five studies met the inclusion criteria for review. Most (14) studies originated from the United States, and there were three from Canada, two from Switzerland, and one each from Israel, Spain, the United Kingdom, and Iran. Two review articles were also included.

- Approximately half of the studies (48%) investigated stand-alone treatments (cannabis and ketamine), while the other half (52%) investigated adjunct treatments (MDMA, LSD, and psilocybin). The most investigated drug was ketamine, which accounted for 28% of the studies. Ketamine studies focussed on the treatment of depression (20%) and PTSD (8%). Cannabis and psilocybin each accounted for 20% of the studies. Cannabis was used mainly as a treatment for PTSD (16%), and to a

lesser degree for anxiety (4%). Psilocybin was used in combined anxiety/depression studies (12%), and in separate anxiety (4%) and depression (4%) studies. Finally, MDMA and LSD each accounted for 16% of the studies. MDMA was used only as a treatment for PTSD, while LSD was used for anxiety (4%) and combined anxiety/depression (12%).

- Overall, the quality of the studies was mixed, with some high and some poor quality studies, and all but one category of evidence was allocated an 'Unknown' ranking. Ketamine for depression was the only category of evidence to be allocated a 'Promising' ranking.

- The key findings for stand-alone treatments were that:

  o the evidence for cannabis in treating PTSD received an 'Unknown' ranking

  o the evidence for cannabis in treating anxiety received an 'Unknown' ranking

  o there was no evidence for cannabis in treating depression

  o the evidence for ketamine in treating PTSD received an 'Unknown' ranking

  o there was no evidence for ketamine in treating anxiety

  o the evidence for ketamine in treating depression received a 'Promising' ranking.

- The key findings for adjunct treatments were that:

  o the evidence for MDMA in treating PTSD received an 'Unknown' ranking

  o there was no evidence for MDMA in treating anxiety

  o there was no evidence for MDMA in treating depression

  o there was no evidence for LSD in treating PTSD

  o the evidence for LSD in treating anxiety received an 'Unknown' ranking

  o the evidence for LSD in treating depression received an 'Unknown' ranking

  o there was no evidence for psilocybin in treating PTSD

  o the evidence for psilocybin in treating anxiety received an 'Unknown' ranking

- o the evidence for psilocybin in treating depression received an 'Unknown' ranking

- o gamma-hydroxybutyric acid (GHB) has not been discussed in the published literature as a treatment for PTSD, anxiety, or depression.

- Despite these rankings, the findings of this review do, however, provide some guidance on where future research efforts could be directed should there be interest in this area.

- There is an opportunity for funders and researchers to consider high quality research, particularly in the areas of MDMA as an adjunctive treatment for PTSD, and cannabis as a treatment for PTSD, sleep disturbance, and nightmares.

- Research of this nature, where safety concerns have been fully investigated and evaluated, may ultimately increase the range of treatments available to those who develop PTSD.

Introduction

Hallucinogens constitute a broad group of psychoactive substances that share an ability to produce sensory distortions and hallucinations at doses that are not otherwise toxic to the body.[1] Hallucinogens primarily act to alter cognition and perception, which is experienced by users as an alteration to ordinary conscious experience.[2] In the current review, hallucinogens are considered as treatments for PTSD, anxiety, and depression. The hallucinogens investigated in this review are cannabis, 3,4-methylenedioxymeth-amphetamine (MDMA), lysergic acid diethylamide (LSD), psilocybin, ketamine, and gamma-hydroxybutyric acid (GHB). While cannabis is often considered separately to other hallucinogens based on their molecular distinction, cannabis does have the ability to alter perception and produce euphoria. However, the perceptual-emotional experiences and physiological effects of cannabis are comparatively less intense than the other hallucinogens.[1] Cannabis has been attributed hallucinogenic properties, including seeing colours or objects as more intense, and the experience of hallucinogenic ideation.[3,4] As such, cannabis was included in the current review of hallucinogens as treatments for PTSD, anxiety, and depression.

Clinical research investigating the therapeutic application of hallucinogens was prominent in the 1950s and 1960s, addressing such conditions as substance dependence and the psychological suffering associated with terminal illness, including anxiety and depression.[5] Following several decades of dormancy, there has been a recent renewal of interest in the use of hallucinogens as treatments for a range of psychiatric disorders. There are at least three reasons why hallucinogens may be considered as a treatment (or adjunctive treatment) for PTSD, anxiety, and depression. First, some people experience treatment resistance to standard psychotherapy. Despite the established efficacy of gold standard PTSD treatments such as prolonged exposure therapy[6], existing therapies have been associated with high rates of dropout and non-responsiveness.[7] Second, compared to currently used medications, hallucinogens are rapid-acting. For example, ketamine use has been shown to alleviate depression and suicidality within 40 minutes, compared to the weeks or months for antidepressants to reduce such symptoms.[8] While the effects are largely transient, acute reduction of symptoms may have important clinical applications in emergency situations. Finally, some hallucinogens appear to enhance the therapeutic process itself, for example, MDMA has been shown to strengthen the therapeutic alliance due to its prosocial effects.[9] Therefore, hallucinogens are worthy of enquiry as a possible adjunct to standard treatment approaches.[10]

The aim of this REA is to examine the scientific literature for evidence of effectiveness of six types of hallucinogens - cannabis, ketamine, MDMA, LSD, psilocybin, and GHB - as treatments for adult populations with PTSD, anxiety, or depression diagnoses or symptoms. Cannabis and ketamine are generally used as stand-alone treatments for the treatment of PTSD, anxiety and depression, while LSD and MDMA are used as adjuncts to psychotherapy for PTSD, anxiety and depression. Psilocybin has been trialled as both a stand-alone and an adjunct treatment for PTSD, anxiety and depression. Currently there are no guidelines or systematic reviews pertaining to this topic. An overview of the use of the six types of hallucinogens as emerging interventions for the treatment of PTSD, anxiety, and depression, and their respective levels of evidence support, is given below.

Cannabis

Cannabis, also known as marijuana, is the name of a group of plants that produce the chemical tetrahydrocannabinol (THC). THC is the main psychoactive component of cannabis, and along with many other constituents of cannabis, is referred to as a 'cannabinoid'.[11] To date, at least 134 chemically diverse synthetic versions of cannabinoids have been created by scientists, as pharmacological tools to study the endogenous cannabinoid system, and also by manufacturers of illegal drugs.[12] Natural cannabis is generally preferred by recreational users since it tends to be associated with fewer adverse effects, so the majority of synthetic cannabinoid use is experimental.[12] An example of a synthetic cannabinoid used for research purposes is 'nabilone'.

Cannabinoids operate on the endocannabinoid system (eCB), which is located in the nervous system, and comprises endogenous cannabinoids (chemical compounds synthesised in the body), cannabinoid receptors (CB_1 and CB_2), and enzymes.[13] The eCB regulates a variety of physiological processes including sleep, appetite, pain sensation, mood, and memory, and operates in limbic brain structures such as the basal ganglia, anterior cingulate cortex, amygdala, and hippocampus.

As a treatment for a range of health conditions, cannabis is most often used as a stand-alone treatment, although in most instances patients' regular concomitant medication is maintained during trials.

While users of cannabis can experience desired effects such as more positive or friendly feelings and talkativeness, mild euphoria, intensification of sensory experiences, and relaxation,[14,15] cannabis use can also produce a number of mild-to-moderate side effects. These include dry mouth, dry eyes, headache, orthostatic hypotension, agitation, and sedation.[16-18] There are also ongoing concerns about the long-term use of cannabis having

the potential for adverse psychiatric effects. These include the potential for development of schizophrenia, especially in adolescents, memory impairments, cognition impairments including reduced executive function and visuospatial perception, and impulsivity and suicidality due to hyperactivity of the eCB system.[19] Another potential longer-term effect of cannabis use is altered anticipatory reward processing in the brain, which may increase the risk for continued drug use and later addiction.[20]

The specific risks associated with cannabis use by individuals with PTSD have also been investigated. There is a greater risk of developing or having cannabis use disorder in people with PTSD, and Boden et al explained this phenomenon by suggesting, "(a) the experience of PTSD predisposes affected individuals to use cannabis to cope with negative internal states, (b) discontinuation of cannabis use (even temporarily) paradoxically leads to greater PTSD symptomatology, via withdrawal, resulting in (c) heightened craving for cannabis, and (d) greater cannabis use problems as well as relapse to cannabis use to cope with increased negative internal states".[21] Additionally, a case study of a 24-year-old veteran with PTSD found that medicinal cannabis induced psychosis.[22]

Cannabis and PTSD

The brain structures housing the eCB, such as the hippocampus, amygdala, and prefrontal (PF) and anterior cingulate cortex, have been implicated in PTSD. For example, these structures are thought to play a critical role in stress-induced emotions and aetiology of PTSD.[23] As such, the eCB has been implicated in the pathophysiology of PTSD, which points to a potential role for cannabinoids in its treatment.[16] Individuals with PTSD are known to have smaller hippocampi than non-PTSD controls[16], and animal studies have shown that cannabinoids can promote hippocampal neurogenesis (growth of the hippocampal tissue).[24] Furthermore, individuals with chronic PTSD have been shown to have abnormally functioning CB_1 receptors, such that they have a higher availability of CB_1 receptors and lower concentrations of anandamide, which is an endogenous cannabinoid agonist.[25] Cannabinoids are likely to have an effect on PTSD symptoms through the activation of these unoccupied CB_1 receptors. The CB_1 receptors have also been shown to play an important role in the extinction of aversive memories in mice.[26] In addition, poor sleep quality and nightmares related to PTSD are thought to improve with the use of cannabinoids, due to the modification of sleep architecture. More specifically, cannabinoids tend to deplete rapid eye movement (REM) sleep (the phase of sleep during which nightmares occur) and enhance non-REM stage four sleep (the restoring phase of sleep).[14] Therefore, cannabinoids appear to have the ability to effectively treat a number of PTSD symptoms at the neural level.

Cannabis and anxiety

Similarly to PTSD, anxiolytic (i.e., anti-anxiety) effects of THC are induced through activation of CB_1 receptors, and the reduction of activity in limbic system structures, which is increased in cases of pathological anxiety.[27] Low doses of THC have anxiolytic-like effects whereas higher doses produce anxiogenic (anxiety-increasing) reactions.[28] Therefore, at the neural level, reduced subjective anxiety has been associated with THC-induced changes in the functional activity of brain areas implicated in the processing of anxiety, while molecular mechanisms are as yet unknown.[27]

Cannabis and depression

The understanding of the aetiology of depression has been dominated by the traditional monoamine hypothesis which predicts that the underlying pathophysiologic basis of depression is a depletion in the levels of serotonin, norepinephrine, and/or dopamine in the central nervous system.[29] However, it has also been proposed that depression may be linked to a deficiency in the endocannabinoid system, more specifically, that blocking the cannabinoid CB_1 receptor may be associated with antidepressant effects, and that enhancement of this system could be a novel form of pharmacotherapy for treatment-resistant depression.[30,31] However, the proponents of this theory acknowledge that it is currently speculative and without human clinical data.

Ketamine

Ketamine was originally developed and promoted as a general anaesthetic in 1962, and soon thereafter became a recreational drug of abuse because of its psychedelic properties.[32] More recently it has received attention as a potential treatment for PTSD and depression, based largely on its role as an antagonist of the glutamate *N*-methyl-D-aspartate (NMDA) receptor.[33] LSD and psilocybin are classed as classical hallucinogens which act primarily on the serotonergic system, whereas ketamine is classed as a dissociative anaesthetic which acts primarily on the glutamatergic system.[33,34] Ketamine is still used as a general anaesthetic, and is often used for sedation in the administration of electroconvulsive therapy (ECT). While its safety profile makes it an important medicine in anaesthesia and pain management[35], there are physical and psychological risks associated with ketamine use. Acute risks are remote, however acute ketamine poisoning, acute cardiac events, death from an acute dose, and a resurgence of psychotic symptoms in patients with schizophrenia have been reported.[35] Chronic and frequent use of ketamine has been robustly associated with physical harm including ketamine-induced ulcerative cystitis, kidney dysfunction, and 'k-cramps' (intense abdominal pain).[35] Furthermore, long-term, frequent usage has been

associated with increases in depression (contrasted with experimental doses for reducing depressive symptoms which are administered infrequently), impairments in memory, planning, and frontal functions, neurological changes such as white matter abnormalities, and the risk of addiction.[35]

The aim of the current review is to examine the potential of ketamine as a stand-alone treatment, therefore trials which examined the administration of ketamine as an anaesthetic for ECT were not included.

Ketamine and PTSD

The potential for the use of ketamine in the treatment of PTSD is based on accumulating evidence for the role of glutamate (an excitatory neurotransmitter) in mediating stress responsivity, the formation of traumatic memories, and the pathophysiology of PTSD.[36] While biological mechanisms underlying the effects of ketamine in patients with PTSD are unknown, there are several hypotheses that involve the glutamatergic system and the PF cortex. Chronic stress has been shown to disrupt glutamate transmission in the PF cortex, and animal studies have demonstrated reductions in synaptic density and complexity in the PF cortex and hippocampus secondary to chronic stress. More recently, ketamine has been shown to rapidly increase the number and function of synaptic connections in the PF cortex, with an accompanying rapid reversal of behavioural and neuronal changes resulting from chronic stress in rats, partially through stimulation of brain-derived neurotrophic factor (BDNF) signalling.[36]

Ketamine and anxiety

There were no published studies investigating ketamine as a treatment for anxiety, however evidence is emerging for the efficacy of ketamine as a treatment for obsessive-compulsive disorder (OCD[1]).[4] There is converging evidence which suggests a role for the glutamate system in the pathophysiology of OCD (the glutamatergic hypothesis of OCD), and in a recent randomised controlled trial (RCT), ketamine's action as a glutamate receptor antagonist was believed to be a mechanism involved in the reduction of OCD symptoms.[37]

Ketamine and depression

Compared to PTSD, more is known about the antidepressant effects of ketamine. Key to the mechanisms of ketamine as an antidepressant is neuroplasticity (a collection of events

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[1] OCD has been removed from the Anxiety Disorder section in the Diagnostic and Statistical Manual for Psychiatric Disorders - Version 5 (DSM-5) and into a classification group called Obsessive-Compulsive and Related Disorders. It has been included in our review as it has traditionally been considered an anxiety disorder

which are critical for neuronal adaptation), and glutamate.[38] Altered glutamatergic transmission, which is thought to promote neuroplastic deficits, has been implicated in the pathophysiology of depression.[33,38] Ketamine appears to enhance neuroplasticity by initiating a glutamatergic response via its antagonistic action on NMDA glutamate receptors, ultimately activating AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, and raising the level of BDNF, thus normalising these neuroplastic deficits.[8,33,39] Depression is also associated with deficient neurogenesis and neurotrophic activity, and BDNF levels are decreased in depressed patients and normalised after antidepressant treatment.[40] The mechanisms underlying the effects of ketamine (the simultaneous blockade of NMDA receptors and activation of AMPA receptors), are integral for the induction of the antidepressant response[41], which is supported by findings that NMDA glutamate receptors play an important role in the mechanism of action of antidepressants.[33] Therefore, a possible therapeutic mechanism of ketamine is glutamate-induced neuroplasticity.[33] Such neuroplastic adaptations are thought to normalise the PF-limbic circuitry, which is subject to dysfunction in depression.[42]

MDMA

The main component of the drug 'ecstasy', MDMA is a synthetic compound that alters mood and perception and induces a brief experience that is typically characterised by euphoria, increased wellbeing, sociability, self-confidence, and extroversion, with users reporting having decreased feelings of fear while maintaining a clear-headed and alert state of consciousness.[43] While cannabis acts on the eCB (which includes the amygdala), MDMA acts largely on the amygdala itself. In addition, MDMA alters neurotransmitter and neuropeptide activity.

In addition to producing the desirable effects described above, there can be risks associated with uncontrolled MDMA use. The acute and longer-term medical risks of use outlined in the literature include hyperthermia (dangerously high body temperature), hyponatremia (dangerously low plasma sodium level), the serotonin syndrome (excessive release of serotonin which is accompanied by symptoms such as confusion, difficulty walking, muscle jerks, and poor control of heart rate and blood pressure), cardiac complications, liver abnormalities, and neurological complications.[44] Further, there is some evidence to suggest that psychological risks, including depression, memory problems, anxiety, mood fluctuation, and poor concentration are associated with the extent of MDMA use, such that the greater the number of occasions of use, the greater the incidence of the problem.[45]

MDMA and PTSD

MDMA has recently been trialled as an adjunct to psychotherapy for PTSD. The usefulness of MDMA as an adjunct, rather than as a stand-alone treatment, is thought to stem from its ability to help patients overcome obstacles to successful therapy, and that the MDMA experience itself, rather than simply the pharmacological effects of the drug, might assist with remission of treatment-refractory PTSD.[46]

The first mechanism by which MDMA is thought to decrease PTSD symptoms is via the amygdala. The amygdala is a key brain structure involved in the acquisition and storage of fearful memories, and is controlled by inhibitory brain circuitry which includes the ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex, and the hippocampus.[9,47] According to the neurocircuitry model of PTSD, abnormal patterns of activity in the amygdala and its inhibitory circuitry are implicated in the disorder.[48] More specifically, people with PTSD have increased amygdala activity and deficient inhibitory circuitry which together manifest in the exaggerated and uncontrolled fear response characteristic of PTSD. MDMA appears to trigger changes in brain activity which may address these abnormalities, by increasing activity in the inhibitory circuitry and decreasing activity in the left amygdala.[49] The resultant reduction in the fear response is thought to facilitate the processing of traumatic material during psychotherapy by enhancing the ability to tolerate intense affect.[9] One reason that some individuals may not benefit from psychotherapies is their inability to tolerate the necessary level of engagement with traumatic memories.[50] Therefore, reducing the fear response may enable patients to stay emotionally engaged without being overwhelmed by anxiety, improving the effectiveness of psychotherapies.

The second mechanism by which MDMA is thought to decrease PTSD symptoms is via neurotransmitter and neuropeptide activity. Neurotransmitters and neuropeptides are chemical messengers that transmit signals between cells.[51] MDMA triggers the release of various neurotransmitters, most notably serotonin, which has effects on mood and perception.[49] Since there is evidence for diminished serotonin release in PTSD which can manifest in aggression, impulsivity, depression, and suicidality,[52] the increased availability of serotonin is a possible mechanism for MDMA-induced reductions in PTSD symptoms. MDMA also increases circulating neuropeptides, most notably oxytocin, which is associated with prosocial effects such as affiliation, bonding, and trust.[53] These effects may assist with strengthening the therapeutic alliance, which is recognised as being crucial for recovery from PTSD.[9] Therefore, MDMA is thought to be an effective addition to psychotherapy for treating PTSD via its neurophysiological effects, and its influence on the psychotherapeutic process itself.[9]

Taken together, these MDMA-induced neurophysiological changes are thought to reduce fear while increasing interpersonal trust in the psychotherapeutic process, and thus contribute to decreases in PTSD symptomatology.[9]

MDMA and anxiety

There is very little literature that has examined whether MDMA may have anxiolytic effects. However, rodent studies provide insight into possible mechanisms by which MDMA might reduce anxiety symptoms.[54,55] For example, Leon and Cardenas[54] suggested that MDMA might act as an enhancer of coping strategies in mice, and that the anxiolytic-like effect of MDMA suggests a change in the emotional valence of potential aversive stimuli so that it is 'reinterpreted' as normal stimuli, possibly by dopaminergic mediation.

MDMA and depression

The potential to treat depression with MDMA is based on the monoamine hypothesis.[56] As described earlier, the monoamine hypothesis predicts that the underlying pathophysiologic basis of depression is a depletion in the levels of serotonin, norepinephrine, and/or dopamine in the central nervous system.[29] However, in a recent review, Patel and Titheradge[56] reported that experimental evidence of antidepressant action of MDMA is low, comprising one rodent study and one human volunteer study. They did, however, highlight that MDMA has the potential to act as a rapid-onset antidepressant via its modulation of the 5-HT (serotonin) system, and as an augmentation strategy in cognitive therapy.

LSD

LSD, also known as 'acid', is a semisynthetic drug derived from ergot, a grain fungus.[2,57] Categorised as a classical hallucinogen, it alters the functioning of the serotonergic system, which is implicated in anxiety and depressive disorders.[34] Like MDMA, LSD is used as an adjunct to psychotherapy rather than as a stand-alone treatment. Given in a psychotherapeutic context, LSD facilitates a psychedelic state, intensified emotions, and a deeper self-awareness, all of which alter how the participant encounters their own "inner realities".[58] Psychotherapy sessions that follow the experimental drug sessions serve to integrate participants' experiences and deepen the therapeutic process. However, there are undesired acute effects of LSD which include incidence of negative mood qualities, anxiety, intense feelings of inferiority, guilt, aggressive feelings, panic, a profound fear of death, and suicidal ideation.[59] Relatively less is known about the chronic effects of LSD[60], although it is not considered to be addictive.[61] One possible long-term consequence, which is applicable to all hallucinogens, is hallucinogen persisting perception disorder (HPPD).[62] HPPD is

defined in the Diagnostic and Statistical Manual for Psychiatric Disorders - Version 5 (DSM-5) as a condition in which a person, after the cessation of intake of hallucinogens, re-experiences certain disturbing visuals which were experienced while intoxicated with the hallucinogen. In other words, it is a visual disorder which is a result of assimilation of hallucinogens. Furthermore, long-term use of LSD is associated with increased risk of mental illness including schizophrenia and depression.[61,63]

LSD and PTSD

There have been no clinical trials using LSD to treat PTSD.[4] It has been noted, however, that LSD has mood elevating and prosocial effects which may be useful in the therapeutic process itself.[64]

LSD and anxiety

LSD acts primarily through agonistic actions at several 5-HT (serotonin) receptors, including $5\text{-HT}_{1A/2A/2C}$.[33] Serotonin is a neurotransmitter which is thought to contribute to feelings of wellbeing and happiness. Animal models and clinical studies have shown that 5-HT_{1A} receptor agonists have anxiolytic properties, and $5\text{-HT}_{2A/2C}$ receptor agonists reduce anxiety-related behaviour in animals.[40] It has also been suggested that the altered state of consciousness produced by LSD would create a disruption or interruption of the repetitive, rigid, and pathological pattern of negative and compulsive thoughts present in anxiety disorders, contributing to mental flexibility and changes in perspective and behaviour.[65]

LSD and depression

The antidepressant mechanism of LSD is thought to be largely attributed to its agonistic actions at 5-HT_{2A} receptors.[33] It is possible that the downregulation of 5-HT_{2A} receptors, which occurs as a result of LSD's agonistic actions, might underlie some of the therapeutic effects of hallucinogens in the treatment of depression and anxiety.[33,66] In favour of this hypothesis, 5-HT_{2A} receptor density was found to be increased in the PF cortex in patients with major depression, and to be reduced after chronic treatment with various antidepressants.[33] 5-HT_{2A} receptor activation may also lead to neuroplastic adaptations in the PF-limbic network, which is a mechanism common to LSD and ketamine. Ketamine-induced neuroplastic adaptations, however, occur primarily via the glutamatergic, rather than the serotonergic, system.[33] Neuroplasticity is discussed in the ketamine section below.

Psilocybin

Psilocybin occurs naturally in some species of mushroom, commonly referred to as 'magic mushrooms'.[67] The psychedelic experience of psilocybin is similar to that of LSD but is considered more visual and euphoric, less emotionally intense, and less likely to produce panic and paranoia.[68] Like LSD, psilocybin is categorised as a classical hallucinogen, and similarly acts as an agonist in the serotonergic system after being metabolised to psilocin.[69] Psilocybin acts on multiple serotonin receptors ($5-HT_{1A/2A/2C}$) but exerts a psychedelic effect primarily through its influence on serotonin $5-HT_{2A}$ receptors.[70] Psychedelic experiences have been associated with sustained increases in wellbeing and optimism[71] and reduced anxious, depressive, and obsessive-compulsive symptoms.[67,72] While psilocybin is thought to have very low physiological toxicity, and is not associated with compulsive drug seeking, it sometimes produces acute and, more rarely, persisting adverse psychological reactions.[73] Psilocybin users' subjective assessments of the drug's enduring consequences include spontaneous alterations of consciousness and flashbacks, during which they re-experience aspects of the hallucinogenic effects, and negative changes in psychological well-being and/or mental functions including concentration problems, mood swings, memory problems, and being pensive and introverted.[73,74] Other potential, but rare, prolonged adverse reactions include persisting psychosis or depression.[74]

Psilocybin has been trialled as both an adjunct to psychotherapy and as a stand-alone treatment. As an adjunct, psilocybin dosing sessions are followed by integrative psychotherapy. The integrative sessions aim to consolidate the memory of the experience and to continue the process of psychological integration, with therapeutic benefits thought to accrue from psilocybin-induced subjective or 'mystical' experiences.[75] As a stand-alone treatment, psilocybin administration is usually accompanied by psychological support (but not psychotherapy), where psychiatrists are present during dosing sessions to provide non-directive support and the patient is allowed to experience an uninterrupted "inner journey".[69]

Psilocybin and PTSD

There have been no clinical trials using psilocybin to treat PTSD.[4] However, neuroscience and preclinical findings indicate feasibility for the use of psilocybin to reduce PTSD symptomatology. More specifically, psilocybin was found to reduce amygdala reactivity in humans during emotion processing[76], and also to increase hippocampal neurogenesis and facilitate extinction of a fear response in mice.[77]

Psilocybin and anxiety

Animal models suggest that the rapid anxiolytic effect of serotoninergic psychedelics occurs as a result of downregulation of 5-HT$_{2A}$ receptor activity.[33] This hypothesis is consistent with findings that demonstrate reduction of 5-HT$_{2A}$ receptor density as a result of sustained anti-depressant treatments.[78] In the case of obsessive-compulsive disorder (OCD), serotonin (5-HT) reuptake inhibitors (i.e., selective serotonin reuptake inhibitors (SSRIs) and clomipramine) are currently among the most effective pharmacologic treatments available for OCD, while some 5-HT$_2$ antagonists can bring on OCD symptoms.[79] Such findings support the central role of serotonin in OCD, which lends support to the potential benefit derived from psilocybin.

Psilocybin and depression

Currently available antidepressant medications (i.e., SSRIs) act indirectly on 5-HT$_{2A}$ receptors, whereas psilocybin works as a direct 5-HT$_{2A}$ agonist, which is why it has attracted particular interest as a novel pharmacology for depression.[69]

The action of psilocybin on the glutamate system may explain some of its anti-depressant effects.[75] Serotonergic psychedelics in rodent studies have been associated with enhanced cortical glutamatergic transmission, specifically, enhanced activation of cortical AMPA receptors and increased expression of BDNF messenger ribonucleic acid (mRNA) in neocortical areas.[80,81] These same effects have elsewhere been identified as biomarkers of anti-depressant effects in humans. For example, decreased cortical BDNF is associated with major depression in humans[82], while anti-depressant treatment has been shown to normalise cortical BDNF.[83]

Another mechanism of action may be at the level of brain structure and network connectivity.[75] Psilocybin demonstrates decreased medial PF cortex activity.[84] Neuroimaging research has shown an association between depressive symptoms and increased activity in the medial PF cortex[85], while antidepressants normalise medial PF cortical activity.[86] Further, patients with major depression show increased default mode network (DMN) connectivity[87], while psilocybin decreases connectivity within the DMN.[84]

GHB

GHB was formerly used as a hypnotic and anaesthetic agent.[88] It has not been discussed in the published literature as a treatment for PTSD, anxiety, or depression. Rather, more recently GHB has been discussed as a potential treatment for alcohol withdrawal. In 2010, a Cochrane review examined the efficacy and safety of GHB as a treatment for alcohol

withdrawal.[89] This review found that there was insufficient evidence to be confident that GHB is more or less effective as a treatment for alcohol withdrawal, as other drugs. Consideration of literature related to the efficacy of GHB for alcohol withdrawal is beyond the scope of the current review.

Method

This literature review utilised a rapid evidence assessment (REA) methodology. The REA is a research methodology which uses similar methods and principles to a systematic review but makes concessions to the breadth and depth of the process, in order to suit a shorter timeframe. The advantage of an REA is that it utilises rigorous methods for locating, appraising, and synthesising the evidence related to a specific topic of enquiry. To make an evidence assessment rapid, however, the methodology places a number of limitations in the search criteria and in how the evidence is assessed. For example, REAs often limit the selection of studies to a specific time frame (e.g., last 10 years), and limit selection of studies to peer-reviewed published, English studies (therefore not including unpublished pilot studies, difficult-to-obtain material, and/or non-English language studies). Also, while the strength of the evidence is assessed in a rigorous and defensible way, it is not necessarily as exhaustive as a well constructed systematic review and meta-analysis. A major strength, however, is that an REA can inform policy and decision makers more efficiently by synthesising and ranking the evidence in a particular area within a relatively short space of time and at less cost than a systematic review/meta-analysis.

Defining the research question

The components of the question were precisely defined in terms of the population, the interventions, the comparisons, and the outcomes (PICO – refer to Appendix 1). Operational definitions were established for key concepts for each question, and from this specific inclusion and exclusion criteria were defined for screening studies for this REA. As part of this operational definition, the population of interest was defined as healthy adult patients (i.e., not suffering from a life-threatening disease) with PTSD, anxiety, or depression (or subclinical features of one or more of these disorders); the intervention was defined as the administration of cannabinoids, MDMA, LSD, psilocybin, ketamine, or GHB for the treatment of PTSD, anxiety, or depression; and the mental health outcomes were defined as improvements in PTSD, anxiety, or depression symptoms.

Search strategy

To identify the relevant literature, systematic bibliographic searches were performed to find relevant trials from the following databases: EMBASE, PubMed, PsychINFO, and The Cochrane Library.

A Cochrane review and several systematic reviews with meta-analyses were identified which examined the effectiveness of ketamine in the treatment of depression.

Search terms

Search terms specific to the drugs, psychiatric disorders, and treatments of interest were included in searching the Title/s, Abstract/s, MeSH terms, and Keywords lists:

Cannabidiol, Cannabinoid, THC, cannabis extract*, DELTA9-THC, DELTA9-tetrahydrocannabinol, tetrahydrocannabinol, CBD, Epidiolex, MDMA, methylenedioxymethamphetamine, 3,4-methylenedioxymethamphetamine, ecstasy, molly, LSD, lysergic acid diethylamide, psychedelic*, Psilocybin OR "magic mushroom*, mushroom, ketamine, GHB, Gamma-Hydroxybutyrate, sodium oxybate, Xyrem, Posttraumatic stress disorder, PTSD, depression, major depression, anxiety, generali*ed anxiety, Intervention, pharmacologic*, treatment, pharmacotherapeutic, therapy, medication, psychopharmacology.

An example of the search strategy conducted in the Embase database appears in Appendix 2.

Paper selection

Papers were included in the review of the evidence if they met all of the following inclusion criteria.

Included:
1. Internationally and locally published peer-reviewed research studies
2. Research papers that were published from inception to **6th July 2017**
3. Human adults (i.e., ≥ 18 years of age)
4. English language
5. Sample consisting of individuals with PTSD, anxiety, or depression
6. Trials where the drug (i.e., cannabinoid, MDMA, LSD, psilocybin, ketamine, or GHB) was used to target the symptoms of PTSD, anxiety, or depression (unipolar)

7. Trials with outcome data that assessed changes in one of the following domains:

   a. PTSD

   b. Anxiety

   c. Depression

8. For ketamine and depression, due to the large amount of literature, only studies which were systematic reviews and meta-analyses, or randomised controlled trials were included

9. For the other drugs and disorders, all study designs were included

Excluded:

1. Non-English papers

2. Papers where a full text version is not readily available

3. Children (mean age of sample ≤ 17 years of age)

4. Validation study

5. Animal studies

6. Grey literature (e.g., media: websites, newspapers, magazines, television; conference abstracts; theses)

7. No quantitative outcome data reported

8. For ketamine and depression, due to the large amount of literature, papers which were non-RCT design or non meta-analytic were excluded

9. For trials examining ketamine and depression, due to the vast amount of literature, studies which examined ketamine in conjunction with another therapy [e.g., electroconvulsive therapy (ECT) or another anti-depressant] were excluded

Information management

A screening process was adopted to code the eligibility of papers acquired through the search strategy. Papers were directly imported into the bibliographic tool Endnote X5. Screening for duplicates was performed in Endnote. References were then imported into Covidence for screening and for full text review.

All records that were identified using the search strategy were screened for relevance against the inclusion criteria. Initial screening for inclusion was performed by one reviewer using Covidence, and was based on the information contained in the title and abstract. Full text versions of all studies which satisfied this initial screening were obtained.

In screening the full text paper, two independent reviewers made the decision on whether the paper should be included or excluded, based on the pre-defined inclusion and exclusion

criteria. If the paper met the criteria for inclusion, then it was subject to data abstraction. It was found that there was 90% inter-rater agreement between the two reviewers. Differences of opinion were resolved through discussion, and the final set of articles was agreed upon by both reviewers. The following information was extracted from studies that met the inclusion criteria: (i) study description, (ii) intervention description, (iii) participant characteristics, (iv) primary outcome domain, (v) main findings, (vi) bias, and (vii) quality assessment.

Evaluation of the evidence

There were five key components that contributed to the overall evaluation of the evidence[90]:

1. The **strength of the evidence base**, in terms of the quality and risk of bias, quantity of evidence, and level of evidence (study design)

2. The **direction** of the study results in terms of positive, negative, or null findings

3. The **consistency** of the study results

4. The **generalisability** of the body of evidence to the target population (i.e., adults/military personnel)

5. The **applicability** of the body of the evidence to the Australian context.

The first three components provided a gauge of the internal validity of the study data in support of efficacy for an intervention. The last two components considered the external factors that may influence effectiveness, in terms of the generalisability of study results to the intended target population, and applicability to the Australian context.

Strength of the evidence base

The strength of the evidence base was assessed in terms of: a) quality and risk of bias, b) quantity of evidence, and c) level of evidence.

a) **Quality and risk of bias** reflected how well the studies were conducted, including how the participants were selected, allocated to groups, managed and followed-up, and how the study outcomes were defined, measured, analysed, and reported. An assessment was conducted for each individual study with regard to the quality and risk of bias criteria utilising a modified version of the Chalmers Checklist for appraising the quality of studies of interventions (see Appendix 3). Three independent raters rated each study according to these criteria, and together a consensus agreement was reached as to an overall rating of 'Good', 'Fair', or 'Poor'.

b) **Quantity** of evidence reflected the number of studies that were included as the evidence base for each ranking. The quantity assessment also took into account the number of participants in relation to the frequency of the outcomes measures (i.e., the statistical

power of the studies). Small, underpowered studies that were otherwise sound may have been included in the evidence base if their findings were generally similar – but at least some of the studies cited as evidence must have been large enough to detect the size and direction of any effect.

c) **Level of evidence** reflected the study design. Details of the study designs included in this REA were assessed against a hierarchy of evidence commonly used in Australia[91]:

    a. Level I: A systematic review of RCTs

    b. Level II: An RCT

    c. Level III-1: A pseudo-RCT (i.e., a trial where a pseudo-random method of allocation is utilised, such as alternate allocation)

    d. Level III-2: A comparative study with concurrent controls. This can be any one of the following:

        i. Non-randomised experimental trial [this includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e., utilise A vs B and B vs C to determine A vs C with statistical adjustment for B)]

        ii. Cohort study

        iii. Case-control study

        iv. Interrupted time series with a control group

    e. Level III-3: A comparative study without concurrent controls. This can be any one of the following:

        i. Historical control study

        ii. Two or more single arm study [case series from two studies. This would include indirect comparisons utilised (i.e., A vs B and B vs C to determine A vs C where there is no statistical adjustment for B)]

        iii. Interrupted time series without a parallel control group

    f. Level IV: Case series with either post-test or pre-test/post-test outcomes.

Overall strength

A judgement was made about the strength of the evidence base, taking into account quality and risk of bias, quantity of evidence, and level of evidence. Agreement was sought between

three independent raters and consensus about the strength of the evidence base was obtained according to the following categories.

High strength

One or more level I studies with a low risk of bias OR three or more level II studies with a low risk of bias

Moderate strength

One or two level II studies with a low

risk of bias OR two or more level III studies with a low risk of bias

Low strength

One or more level I to level IV studies with a high risk of bias

Direction

The direction component of the ranking system makes a judgement as to whether the results are in a positive or negative direction. In cases where there are studies which show findings in different directions, preference is given to the direction of the study findings with the highest level and best quality.

Positive direction

The weight of the evidence indicates positive results

Unclear direction

The evidence does not show significant effects OR the results are mixed

Negative direction

The weight of the evidence indicates negative results

Consistency

The consistency component of the ranking system of the body of the evidence assesses whether the findings are consistent across the included studies (including across a range of study populations and study designs). It was important to determine whether study results are consistent to ensure that the results are likely to be replicable or only likely to occur under certain conditions.

All studies are consistent reflecting that results are highly likely to be replicable

Most studies are consistent and inconsistency may be explained, reflecting that results are moderately–highly likely to be replicable

Some inconsistency reflecting that results are somewhat unlikely to be replicable

All studies are inconsistent reflecting that results are highly unlikely to be replicable

Generalisability

This component covers how well the participants and settings of the included studies could be generalised to the target population. Population issues that might influence this component included gender, age or ethnicity, or level of care (e.g., community or hospital).

The population/s examined in the evidence are the same as the target population

The population/s examined in the evidence are similar to the target population

The population/s examined in the evidence are different to the target population, but it is clinically sensible to apply this evidence to the target population

The population/s examined in the evidence are not the same as the target population

Applicability

This component addresses whether the evidence base is relevant to the Australian context, or to specific local settings (such as rural areas or cities). Factors that may reduce the direct application of study findings to the Australian context or specific local settings include organisational factors (e.g., availability of trained staff) and cultural factors (e.g., attitudes to health issues, including those that may affect compliance).

Directly applicable to the Australian context

Applicable to the Australian context with few caveats

Applicable to the Australian context with some caveats

Not applicable to the Australian context

Ranking the evidence

On balance, this next step takes into account the considerations of the strength of the evidence (quantity and risk of bias, quantity of evidence and level of evidence), consistency, generalisability and applicability. The total body of the evidence is then ranked into one of four categories: 'Supported', 'Promising', 'Unknown' and 'Not Supported' (see Figure 1). Agreement on ranking is sought between all three independent raters.

NOTE: If the strength of the evidence was considered to be low, the next steps of rating consistency, generalisability, and applicability were not conducted and the evidence was rated as 'Unknown'.

SUPPORTED Clear, consistent evidence of beneficial effect	**PROMISING** Evidence suggestive of beneficial effect but further research required	**UNKNOWN** Insufficient evidence of beneficial effect and further research is required	**NOT SUPPORTED** Clear, consistent evidence of no effect or negative / harmful effect

Figure 1: Categories within the intervention ranking system

Results

The following section presents the flowchart relating to the number of records identified at each stage of the REA (refer to Figure 2). From all the sources searched, 21 original trials were identified as meeting the inclusion criteria, as well as one additional secondary study reporting on longer-term follow-up, another secondary paper which duplicated most of the results from the original paper, and two meta-analyses, totalling 25 papers.

For ketamine as a treatment for depression, two relevant systematic reviews with meta-analysis were identified. A Cochrane Review of "Ketamine and other glutamate receptor modulators for depression in adults" (from here onwards referred to as the "Cochrane Review") was identified as being underpinned by a high quality systematic review and meta-analysis. This review was selected to underpin the ketamine and depression section of the current REA because it specifically examined the use of ketamine for the treatment of depression in a comprehensive way. The systematic review that underpinned the Cochrane Review has a data inclusion cut-off of January 2015. Therefore we did not examine individual studies published prior to 2015, as they would have been considered within the Cochrane Review.

A more recent high quality systematic review and meta-analysis by Kishimoto et al (from here on known as the "Kishimoto review") examined intravenously administered ketamine, had a search cut-off of August 2015. Therefore the Kishimoto review was also included in the current review since it captured several more recent papers.

Of the 25 studies that met the inclusion criteria for review, most (14) originated from the United States, there were three from Canada, two from Switzerland, and one each from Israel, Spain, the United Kingdom, and Iran. Additionally, there were two review articles. Approximately three quarters (72%) were published in the last five years (2011 to 2016), 12% were published between five and 10 years ago (2005 to 2010), with the remainder (16%) published more than 10 years ago (1972 to 2004).
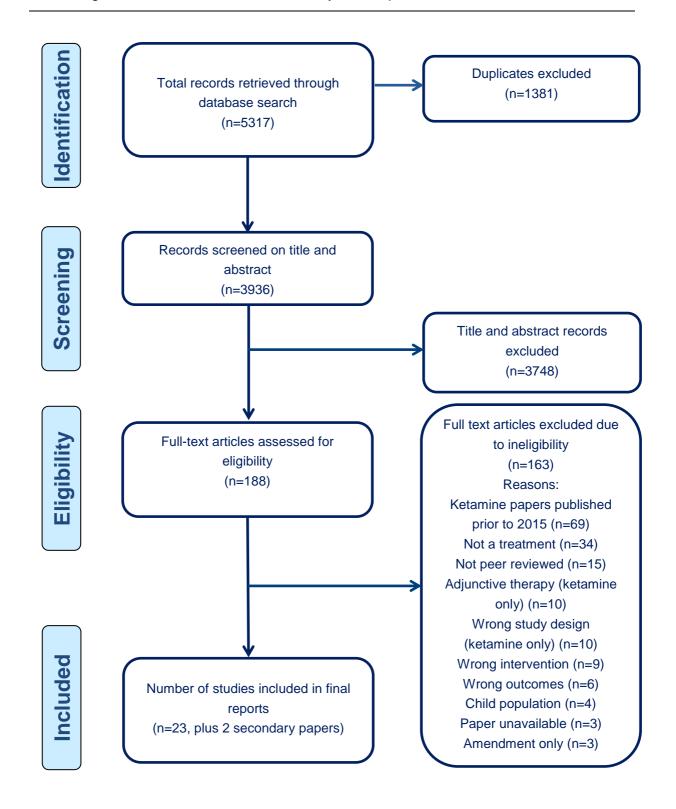
Figure 2: Flowchart representing the number of records retrieved at each stage of the rapid evidence assessment

Summary of the Evidence

A total of 25 articles were included in this review that examined the use of hallucinogens for the treatment of PTSD, anxiety, and depression. A summary of the studies is found in the evidence profile presented in Appendix 4 in detail and in Appendix 5 as a brief overview.

Stand-alone treatments

Cannabis for PTSD

Four studies investigated the effectiveness of cannabis (nabilone and tetrahydrocannabinol (THC)) for the treatment of PTSD and PTSD-related nightmares and insomnia.[16,18,92,93] One of these was a small RCT, one was a small pilot study with no control, and the final two studies were retrospective chart reviews.

The first study was a double-blind, placebo controlled cross-over RCT which was designed to assess the effectiveness of nabilone for treating PTSD-related nightmares in a sample of Canadian male military personnel (N = 10).[18] Frequency, but not intensity, of nightmares using a CAPS assessment was significantly reduced for the nabilone group post-treatment, however, no follow-up data was collected.

A second small (N = 10) open label Israeli pilot study involving a community sample with no control group used THC to treat chronic PTSD.[92] Significant reductions were reported in hyperarousal symptoms, but not overall CAPS score, and there were significant improvements in self-reported nightmare frequency and sleep quality.

The final two studies were Canadian retrospective chart reviews which evaluated past use of nabilone for treating PTSD-related nightmares and insomnia. The first comprised an all-male sample (N = 104) of inmates from a secure treatment unit[16], and the second comprised males and females experiencing treatment-resistant PTSD-related nightmares.[93] In these two retrospective studies there were significant post-treatment improvements in self-reported and subjective measures of insomnia and nightmare frequency and intensity.

Overall, the strength of the evidence for cannabis to treat PTSD and PTSD-related symptoms was found to be low. This rating was based on there being a single small RCT with no follow-up data, while the remaining three studies either lacked a control group or were based on retrospective data. The direction, consistency, generalisability, and applicability of the evidence were not rated because of the lack of strength of the evidence base. Therefore, the body of evidence for cannabis and PTSD was ranked as 'unknown'.

Cannabis for anxiety

One US study investigated the effectiveness of cannabis (nabilone) for treating anxiety in a group of patients from a private psychiatric clinic, and reported significant improvements in clinician-rated anxiety.[17] Although this was a double blind study with a placebo control group, it was a small sample (N = 20) and was not randomised, therefore the strength of the evidence was judged to be low. Consequently, the direction, consistency, generalisability, and applicability of the evidence were not rated, and the body of evidence for cannabis and anxiety was ranked as 'unknown'.

Cannabis for depression

There were no studies identified which used cannabis for the treatment of depression.

Ketamine for PTSD

There were two studies reporting on the use of ketamine for PTSD, one of which was a cross-over RCT, while the other was a case study.[36,94]

The first study was a cross-over RCT (N = 41) in which intravenous ketamine (n = 22) was compared with an active placebo (n = 19) to treat chronic PTSD.[36] Self-reported reductions in PTSD symptom severity by ketamine recipients was significantly greater than those reported by placebo recipients 24 hours post-infusion, however, mean CAPS scores seven days post-infusion did not differ between groups. The second paper was a case study in which a 26-year-old male combat veteran with comorbid PTSD and chronic major depressive disorder (MDD) received one intravenous dose of ketamine.[94] He subjectively reported improvements in anxiety, depression, restorative sleep, and nightmare events, but these were not measured formally. After 14 days he began to relapse into his pre-infusion state of depression.

The strength of the evidence for ketamine as a PTSD treatment was found to be low. This rating was based on there being a single small RCT which did not report follow-up data, and one case study. Consequently the direction, consistency, generalisability, and applicability of the evidence were not rated, and the body of evidence for ketamine as a treatment for PTSD therefore ranked as 'unknown'.

Ketamine for anxiety

There were no studies identified which used ketamine for the treatment of anxiety.

Ketamine for depression

The evidence for using ketamine as a treatment for depression comprised two meta-analyses[39,95] and three original papers.[8,96,97]

A high quality meta-analysis was identified, in the form of a Cochrane review undertaken by Caddy and colleagues, examining data from single or double-blind RCTs to compare adult depression outcomes between glutamate receptor modulators and control conditions.[39] Nine of the 25 studies reviewed referred specifically to the use of ketamine delivered either intravenously or intranasally. Among the included studies, intravenous ketamine treatment was the sole glutamate receptor modulator to demonstrate efficacy above that of placebo. Higher numbers of clinical responders were noted in ketamine conditions compared to midazolam (a type of anaesthetic) at 24 hours, 72 hours, and one week post-infusion. However, the lasting effects of ketamine use were undetermined at two weeks post-infusion. In contrast to active and inactive placebos, ketamine elicited more confusion and emotional blunting and was perceived to be less tolerable than active placebo control (midazolam). Caddy and colleagues[39] noted that long-term efficacy of glutamate receptor modulators, in particular ketamine, is unclear with limited support for symptom improvement at one to two weeks post-infusion. The authors add that the global quality of evidence is limited due to small sample sizes and risk of experimental bias. Adverse events included blood pressure and heart rate changes. Further, many trials did not provide information on all pre-specified outcomes, and salient issues such as suicidality, cognitive, and dropout rates due to adverse effects and the intravenous nature of ketamine were infrequently acknowledged.

In another more recent meta-analysis, Kishimoto and colleagues[95] meta-analysed 14 parallel-group or cross-over RCTs, nine of which compared single intravenous infusions of ketamine versus placebo/pseudo-placebo in patients with MDD. They concluded that a single infusion of ketamine had ultra-rapid efficacy for MDD, lasting for up to one week. Ketamine reduced depression significantly more than placebo/pseudo-placebo beginning at 40 minutes, peaking at day one and losing superiority by days 10-12.

Consistent across the meta-analysis papers were findings that ketamine acted rapidly to reduce depressive symptoms, as quickly as 40 minutes post-infusion, yet the limited support for symptom improvement beyond two weeks suggests that the efficacy of ketamine is transient.

In addition to the review papers, three recent individual RCT papers were located.[8,96,97]

A large (N = 67) double-blind RCT conducted in the US compared intravenous ketamine with an inactive placebo for treatment-resistant depression in a sample of outpatients.[96] Participants, who were predominantly female (67%), received either placebo (n = 32), or two (n = 18) or three (n = 17) doses of ketamine per week for four weeks. The primary outcome measure was the change in clinician-rated depression from baseline to day 15. The frequency of ketamine dosages did not make a difference in the outcome, however, mean depression scores were significantly improved for both ketamine groups compared to placebo. Further, significantly higher proportions of clinical responders and remitters were identified in both ketamine groups compared to placebo controls. Two adverse events were reported, which were significant anxiety (n = 1) and attempted suicide (n = 1), and common side-effects included headache, nausea, dizziness, and dissociation.

A second study from Iran compared ketamine with diclofenac (an anti-inflammatory drug) for the treatment of depression in chronic pain patients (N = 40, female 75%).[97] In a double-blind, parallel-group RCT, 20 patients received oral ketamine three times a day for six weeks, while 20 patients received diclofenac. Mean score reductions in self-reported and clinician-rated depression were significantly greater for the ketamine recipients compared to the diclofenac recipients at week six. Further, response and remission occurred significantly sooner, and at significantly greater rates at week six for ketamine recipients compared to diclofenac recipients. No serious adverse events were reported, however side effects included blurred vision, tremor, restlessness, nervousness, and a transient loss of appetite.

The third study was a small pilot RCT from the US (N = 10) in which intravenous ketamine was administered to predominantly male (70%) active duty US Marine Corp and Navy personnel who had voluntarily presented to an emergency psychiatric department for suicidality or acute depression.[8] Participants received either a single dose of ketamine (n = 3) or placebo (n = 7). There were significantly greater short-term improvements (between four hours and one week post-infusion) in self-reported suicidality and hopelessness scores for the ketamine group compared to placebo. However, at the two-week follow-up, there were no differences between groups, and there was a large imbalance in group sizes between the conditions.

Consistent with the meta-analyses, two of the individual studies demonstrated rapid yet transient improvements in depressive symptoms from between four hours and 15 days post-infusion[8,96], while one study demonstrated longer-term (six weeks) efficacy of ketamine.[97]

With the inclusion of two meta-analyses and three individual RCTs all of which were generally of good quality, the strength of the evidence was rated as high. The direction of the evidence was rated as positive, as significant improvements in depression were observed in

each paper. Most of the studies consistently reported rapidly occurring, yet transient reductions in depressive symptoms after ketamine administration, however, one demonstrated longer-term efficacy, and no studies reported data beyond six weeks. Therefore, serious questions remain about whether ketamine can be effective beyond the short term. The populations examined in the evidence were mostly similar to the target population, however, in one study participants were chronic pain patients,[97] while another contained a military-only sample of participants who were experiencing suicidality.[8] Nevertheless, there appeared to be a reasonable gender balance among all study participants. It was determined that there is evidence to consider the application of this intervention to the target population. Finally, it was judged that this evidence is directly applicable to the Australian context. The body of evidence for ketamine as a treatment for depression was ranked as 'promising'.

Adjunct treatments

MDMA for PTSD

Three papers reported double-blind RCTs using MDMA for PTSD.[9,43,98] Two studies were similarly designed double-blind RCTs with open-label cross-over options.[9,43] Both trialled the use of MDMA-assisted psychotherapy for chronic PTSD.

The first study, conducted in the US by Mithoefer et al.,[43] reported on the administration of two experimental sessions per participant of psychotherapy with either concomitant MDMA (n = 12), or an inactive placebo (n = 8). Participants were diagnosed with chronic PTSD. Stage 1 of the treatment consisted of two 90-minute preparatory sessions, two experimental sessions lasting 8-10 hours each, and nine integration psychotherapy sessions. Experimental sessions comprised an initial oral administration of MDMA or placebo, after which participants either rested while listening to music, engaged in non-directive therapeutic discussion with the co-therapists, or focussed on introspection. A supplemental dose of MDMA or placebo was administered 2.5 hours after the initial dose. On the morning after each experimental session, a non-drug session was conducted, and a further three non-drug integration therapy sessions were conducted weekly, prior to beginning the same cycle for the second experimental session. A final integration session took place two months after the second experimental session. This meant that that each participant received a total of 11 non-drug psychotherapy sessions. The psychotherapy was manualised, following principles for LSD psychotherapy and Holotropic Breathwork. MDMA recipients showed a significantly greater decrease in clinician-rated PTSD severity and self-reported physical response to stress across post-baseline time points, when compared to placebo controls.

Additionally, ten MDMA recipients no longer met DSM-IV criteria for PTSD compared with two placebo recipients. There were no serious adverse events, however, side effects included dizziness, dry mouth, feeling cold, impaired balance, loss of appetite, tight jaw, and decreased concentration. In a follow-up paper, longer-term data was reported on, from 17 to 74 months (M = 45.4 months, SD = 17.3) after the final experimental session.[99] There was no statistically significant difference between participant long-term PTSD follow-up scores and their previously obtained scores at study exit. Two participants relapsed, however on average, statistically and clinically significant gains in symptom relief were maintained for an average of almost four years after treatment completion.

A second Swiss RCT also trialled MDMA-assisted psychotherapy to treat chronic, treatment-resistant PTSD in a similar fashion as Mithoefer et al.,[43] but with a smaller sample (N = 12) and an active placebo.[9] Participants were randomised to each receive three sessions of psychotherapy plus either full-dose MDMA (n = 8) or low-dose MDMA (n = 4). Participants were permitted to continue existing ongoing psychotherapy with their existing therapists during the trial. The experimental sessions were almost identical to those conducted by Mithoefer et al.,[43] comprising MDMA ingestion, followed by relaxation and listening to music, non-directive discussions between patient and therapists, and focussed body work. Twelve non-drug psychotherapy sessions were delivered to each participant using the same manualised approach as Mithoefer et al.[43] There was a significant reduction in self-reported PTSD symptoms at post-treatment, however, despite the similarities between the two studies, CAPS scores at three weeks post-treatment did not significantly differ between the treatment groups. Additionally, all participants still fulfilled PTSD diagnostic criteria at post-treatment. However, at 12-month follow-up (n = 11), five participants no longer met the diagnostic criteria. Side effects similar to those reported by Mithoefer et al.[43] were experienced in the Swiss study.

The third study was a very small RCT involving an all-female Spanish sample (N = 6) with PTSD related to sexual assault.[98] The planned protocol was not carried out in its entirety as the study was prematurely terminated due to "political pressure". The pressure to shut down the study came from the Madrid Anti-Drug Authority which revoked permission to use the study site. Participants received a single low dose of MDMA or placebo in addition to six non-drug psychotherapy sessions. While reductions in PTSD symptoms were greater for the MDMA group than the placebo group, significance values were not reported due to the small sample size.

The strength of the evidence for the use of MDMA to treat PTSD was rated as moderate. The evidence base comprised a small number of studies involving samples weighted heavily

in favour of females (between 83% and 100%), limiting the generalisability of the results to males. Despite the studies being well conducted, sample sizes were small and results were inconsistent, therefore the direction of evidence was rated as unclear. Finally, the evidence was rated as having direct applicability to the Australian context. Overall, the body of evidence for MDMA as a treatment for PTSD was ranked as 'unknown'.

MDMA for anxiety

There were no studies identified which used MDMA for the treatment of anxiety.

MDMA for depression

There were no studies identified which used MDMA for the treatment of depression.

LSD for PTSD

There were no studies identified which used LSD for the treatment of PTSD.

LSD for anxiety

One Swiss RCT was identified that used LSD-assisted psychotherapy for the treatment of anxiety associated with having a life-threatening illness.[58] This was a double-blinded RCT with an active placebo control group, however, being a pilot study the sample was small (N = 11) and was unequally distributed between experimental (n = 8) and control (n = 3) groups. Each participant had two experimental sessions plus six non-drug psychotherapy sessions. Self-reported anxiety was significantly lower in the LSD group compared to the active placebo group at the two-month follow-up, and these values remained stable at 12-month follow-up.

Two US studies conducted in the early 1970s assessed anxiety and depression outcomes after patients had received LSD-assisted psychotherapy.[100,101] Due to the reporting conventions at the time, the authors did not report a primary focus for the intervention. Rather, they stated that the intervention was targeting both anxiety and depression. Anxiety outcomes will be discussed in the current section, and depression outcomes will be discussed in the following section. The first study was an RCT involving clinically depressed and anxious hospital patients (N = 85) which compared group therapy alone with group therapy plus either low or high doses of LSD.[100] There were no post-treatment differences in anxiety scores for the high versus the low-dose groups, however, compared to therapy alone, anxiety scores were significantly lower for both dosage groups. The second study used LSD-assisted psychotherapy to treat 31 patients for anxiety and depression associated with having life-threatening or terminal cancer.[101] Using a single group design, pre/post

depression and anxiety outcomes were assessed using non-standardised ranking scales developed specifically for this study. Scales were rated by physicians, nurses, family members, therapists, and independent raters, because it was deemed too exhaustive for the cancer patients to complete standardised measures themselves. Pooled and averaged ratings suggested significant post-treatment reductions in anxiety. A secondary paper was published the following year reporting the same results from this study.[102]

The strength of this evidence was found to be low based on the following reasons: (i) the sole study to focus specifically on anxiety was a pilot study which sought to examine the safety and feasibility of LSD. It's limitations included having a small sample size which was divided into unequal groups, and having a sample composed of individuals with grave somatic diseases; and (ii) the two combined anxiety/depression studies lacked non-treatment control groups, did not report long-term follow-up, and also contained small samples which included patients with a life-threatening condition. The implication of having samples comprising individuals with grave illnesses is that the course of the illness (e.g., worsening or improving) may impact psychological parameters independent of the therapeutic intervention. As a consequence of the low rating given to the strength of the evidence, the direction, consistency, generalisability, and applicability of the evidence were not rated. Therefore, the body of evidence for LSD as a treatment for anxiety was ranked as 'unknown'.

LSD for depression

LSD was investigated as a treatment for depression in two US studies[100,101] from the 1970s which are described in the preceding section: LSD for anxiety. The first study[100] reported no post-treatment differences in depression scores for the high versus the low-dose groups, however, compared to therapy alone, depression scores were significantly lower for the high-dose group. The second study[101] reported a significant post-treatment reduction in depression based on a pool of subjective ratings.

The evidence for the use of LSD to treat depression was ranked as 'unknown' for the reasons stated in the preceding section: LSD for anxiety.

Psilocybin for PTSD

There were no studies identified which used psilocybin for the treatment of PTSD.

Psilocybin for anxiety

One US pilot study trialled psilocybin for OCD.[67] Using a single group design, escalating doses of psilocybin were administered to participants (N = 9), with a very low dose inserted

randomly in a double-blind fashion. Therapy was not included as part of the treatment, however, participants were accompanied by sitters during experimental sessions. There were self-reported reductions in OCD symptoms post-treatment, however, assessments were not conducted beyond 24-hours post-ingestion therefore, while psilocybin was fast-acting, the duration of symptom improvement is unknown.

Three further US studies reported on the use of psilocybin for treating anxiety and depression arising in patients diagnosed with potentially life-threatening cancer.[72,75,103] In a similar manner to the section on LSD, anxiety outcomes will be presented in the current section, and depression outcomes will be presented in the following section: Psilocybin for depression.

The first of the three combined anxiety/depression studies was a double-blind cross-over RCT with a fairly balanced gender ratio (N = 51, female 49%).[103] This study compared high-dose psilocybin with an active control (low-dose psilocybin) for depression and anxiety in cancer patients with life-threatening diagnoses. During two experimental sessions approximately seven weeks apart, participants were randomised to receive either low-dose then high-dose, or high-dose then low-dose psilocybin. During the sessions, which were attended by monitors who provided non-directive psychological support, participants spent most of the time lying down with their eyes covered, listening to music and focussing on their inner experiences. Experimental sessions were interspersed with an average of approximately 10 preparatory and integration meetings with session monitors. While reductions in clinician and self-reported anxiety scores were significantly greater for the high-dose-first group compared to low-dose-first group after session one, there were no significant group differences after session two or at the six-month follow-up. However, within-group reductions in anxiety from baseline to six months were significant. Adverse effects included transient increases in blood pressure, nausea or vomiting, and transient episodes of psychological distress, such as anxiety or paranoid ideation, during psilocybin sessions.

The second study was a double-blind cross-over RCT using psilocybin-assisted psychotherapy to treat anxiety and depression in patients with life-threatening cancer.[75] In this study, participants (N = 29, female 62%) were randomised to two dosing sessions approximately seven weeks apart: psilocybin followed by placebo (niacin) (n = 14), or placebo (niacin) followed by psilocybin (n = 15). The dosing session conditions were almost identical to those used by Griffiths et al.[103] All participants received preparatory and post-dosing integrative psychotherapy. Integrative therapy used a combination of supportive psychotherapy, cognitive behavioural therapy (CBT), existentially oriented therapy, and

psychodynamic/psychoanalytic therapy. Prior to the cross-over at week seven, clinician-rated anxiety scores were significantly lower for the psilocybin-first group, compared to the placebo-first group, however, there was no difference between the groups for anxiety beyond cross-over. Longer-term follow-up (26 weeks post cross-over) revealed no group differences in anxiety. Significant within-group reductions in anxiety were reported for the psilocybin-first group at all post-baseline time points, including the final point at 26 weeks post-dose 2. For the placebo-first group, there were either no significant reductions, or transient reductions in anxiety prior to cross-over, however, a significant within-group reduction in anxiety was demonstrated immediately after receiving the psilocybin, and was maintained at the 26-week follow-up. There were no serious adverse events, however, side effects included elevated blood pressure and heart rate, headaches, nausea, and transient anxiety.

The third study was a pilot which compared the use of psilocybin with a placebo for anxiety in patients with advanced-stage cancer, and reported its effect on both anxiety and depressive symptoms as main outcome measures.[72] The predominantly female sample (92%) (N = 12), acted as their own controls, and were provided with two experimental treatment sessions, one psilocybin and one placebo, spaced several weeks apart. During both experimental sessions participants were accompanied by treatment staff, but no therapy was involved. There were significant reductions in self-reported anxiety at one and three months post-treatment which were sustained at six months. No adverse or side effects were reported.

The strength of this evidence was rated as moderate. There were methodological limitations to the single anxiety-only (OCD) study (e.g., no control group, small sample size, no follow-up data), however, the combined anxiety/depression studies included two relatively large RCTs which were well designed and reported follow-up data. All studies reported improvements in anxiety symptoms, however, longer-term significant between-group differences were not achieved by all, therefore the direction of evidence was rated as unclear. This inconsistency in the longer-term outcomes suggests that the results are somewhat unlikely to be replicable. Furthermore, because participants in all studies were cancer patients, it was judged that the evidence was not necessarily generalisable to the target population, that being physically healthy adults. As mentioned in the LSD section above, the worsening or improving of participants' cancer may impact psychological parameters independent of the therapeutic intervention. Additionally, it is unclear how cancer medications (which were not reported in the studies) may have contributed to the outcomes. The evidence was nevertheless deemed to be applicable to the Australian context. Overall, although the evidence is suggestive that this treatment is promising for cancer patients,

there is a lack of evidence for healthy adults. Therefore, the evidence was rated as 'unknown'.

Psilocybin for depression

A single UK study used psilocybin accompanied by supportive, non-directive psychological support for treatment-resistant depression.[69] This was an open-label feasibility trial (N = 12) with no control group, conducted to optimise the protocol for psilocybin administration. Participants received a low dose and a high dose of psilocybin in two separate sessions. Relative to baseline, self-reported depressive symptoms at five post-treatment time points to three months were significantly reduced.

Psilocybin was also investigated as a treatment for both depression and anxiety in three US studies[57,58,87] which were described in the preceding section: Psilocybin for anxiety. The first study[103] reported that reductions in clinician and self-reported depression scores were significantly greater for the high-dose-first group compared to low-dose-first group after session one, there were no significant group differences after session two or at the six-month follow-up. However, within-group reductions in depression from baseline to six months were significant. Adverse effects included transient increases in blood pressure, nausea or vomiting, and transient episodes of psychological distress, such as anxiety or paranoid ideation during psilocybin sessions. In the second study,[75] prior to the cross-over at week seven, clinician-rated depression scores were significantly lower for the psilocybin-first group, compared to the placebo-first group, and at six weeks post-cross-over, depression scores were significantly lower for the psilocybin-first group. Longer-term follow-up (26 weeks post cross-over) revealed no group differences in depression scores. Significant within-group reductions in depression were reported for the psilocybin-first group at all post-baseline time points, including the final point at 26 weeks post-dose 2. For the placebo-first group, there were either no significant reductions, or transient reductions in depression prior to cross-over, however, a significant within-group reduction in depression was demonstrated immediately after receiving the psilocybin and was maintained at the 26-week follow-up. The third study[72] reported a significant reduction in self-reported depressive mood at six months post-treatment.

The strength of this evidence was rated as moderate. There were methodological limitations to the single depression-only study (e.g., lack of control group, small sample size, lack of long-term follow-up data beyond three months), however the combined anxiety/depression studies included two relatively large RCTs which were well designed and reported follow-up data. All studies reported improvements in depressive symptoms, however, longer-term

significant between-group differences were not achieved by all, therefore the direction of evidence was rated as unclear. This inconsistency in the longer-term outcomes suggests that the results are somewhat unlikely to be replicable. Furthermore, because participants in all studies were cancer patients, it was judged that the evidence was not necessarily generalisable to the target population for the reasons mentioned earlier. The evidence was deemed to be applicable to the Australian context. Overall, although the evidence is suggestive that this treatment is promising for cancer patients, there is a lack of evidence for healthy adults. Therefore, the evidence was rated as 'unknown'.

GHB for PTSD

There were no studies identified which used GHB for the treatment of PTSD.

GHB for anxiety

There were no studies identified which used GHB for the treatment of anxiety.

GHB for depression

There were no studies identified which used GHB for the treatment of depression.

Discussion and Implications

The aim of this review was to assess the evidence related to hallucinogenic drug interventions for PTSD, anxiety, and depression in adults. The drugs examined in the review were divided into two categories, stand-alone treatments (cannabis and ketamine) and adjunct treatments to psychotherapy (MDMA, LSD, and psilocybin). While GHB was included in the scope of this review, it has not been discussed in the published literature as a treatment for PTSD, anxiety, or depression, but rather as a potential treatment for alcohol withdrawal. There is a logic for the potential effectiveness of a number of these hallucinogens given their varying mechanisms of action, which in many cases aligns with documented neurobiological vulnerabilities and deficiencies in PTSD, anxiety, and depression.

Overall, the results of the REA showed that the vast majority of evidence for the effectiveness of hallucinogens to treat PTSD, anxiety, and depression was rated as 'Unknown', however there are several findings in this review which are worth further consideration, and which are discussed below. The key limitations of the studies included lack of randomisation, small sample sizes, inconsistent results, and lack of follow-up assessment. Another key limitation is that while adverse responses during the trials or

follow-up periods have been reported in the papers, we do not have information on any longer-term adverse impacts that may reflect cumulative risks associated with these agents.

For the stand-alone treatments, ketamine was ranked as 'Promising' for the treatment of depression. A large volume of literature investigating the use of ketamine for depression has been published. Consistent across the meta-analyses and studies identified in this review was that the effects of ketamine on depression are rapid, yet transient, with limited evidence for reductions in symptoms beyond two weeks. A number of research groups are currently working on finding ways to improve the administration of the drug (i.e., trying to create an effective oral form of the drug, rather than the intravenous administration that is most commonly used), and ways to make the effects of the drug sustained beyond two weeks. It is likely that as further advances are made with this drug, the ranking could shift to 'Supported' if further high quality studies are published. It should also be noted that there is currently an Australian trial underway evaluating the effectiveness of ketamine as a treatment for depression. The small amount of published evidence cited above for ketamine in the treatment of PTSD, consistent with the above, did not indicate a lasting treatment response.

In this review cannabis was investigated as a stand-alone treatment for PTSD and/or PTSD-related nightmares. Although the evidence was ranked as 'Unknown', the studies that pertained to treatment for PTSD-related sleep difficulties and nightmares were of particular interest. Specifically, a single small RCT found that the frequency but not intensity of PTSD-related nightmares was significantly reduced post-treatment, while a small pilot study without a control group found that there were significant improvements in self-reported nightmare frequency and sleep quality. While we acknowledge that the evidence in this area is relatively weak due to the small number and poor quality of studies conducted, the consistency in direction of these study outcomes, particularly in sleep and nightmares, suggests that in this specific area on the basis of this data, cannabis may be a drug that warrants further research and examination. Doing so, however, requires consideration of the concerns raised about the potential adverse effects of long-term cannabis use, for example, the potential development of schizophrenia, particularly in adolescents, memory and cognition impairments, impulsivity and suicidality, and the increased risk of addiction.[19,20]

The evidence for all of the hallucinogens that were used as adjunct treatments to psychotherapy was rated as 'Unknown'. Amongst these, however, the evidence for MDMA suggested that this drug may warrant further research and examination for the treatment of PTSD. MDMA is thought to be an effective adjunct to psychotherapy because it inhibits the fear response, allowing for processing of traumatic memories during therapy, and it has

prosocial effects, which can promote a stronger therapeutic alliance. MDMA-assisted psychotherapy was trialled in two very similarly designed studies and a third very small study. These studies produced consistent findings that self-reported PTSD improved (acknowledging that other measures did not report consistent findings). This suggests that further studies are warranted while giving due consideration to the acute and longer-term medical and psychological risks associated with MDMA use, for example, hyperthermia, hyponatremia, confusion, muscle jerks, cardiac complications, neurological complications, and memory problems.[44,45] These studies also raise questions for future studies. Specifically, given relatively large doses of non-specific psychotherapy are given in the context of MDMA drug administration, it would be interesting to consider the use of more focussed and evidence-based gold standard PTSD treatments such as prolonged exposure or cognitive processing therapy as the adjunct in the context of MDMA administration.

Limitations

The findings from this REA should be considered alongside its limitations. In order to make this review 'rapid', some restrictions on our methodology were necessary. These limitations included: the omission of non-English language papers and reference lists of included papers not being hand-searched to find other relevant studies. Similarly, although we did evaluate the evidence in terms of its strength, consistency, and generalisability, these evaluations were not as exhaustive as in a systematic review methodology. We made a qualitative judgement based on the level of evidence about the certainty of our estimates of prevalence. We did not use a meta-analysis methodology to combine or synthesise the results in a statistical way. Lastly, it is important to consider that our methodology allowed for a wide range of trial methodologies. We included studies that used methodologies such as single case studies or case series designs, which are often excluded from systematic reviews. Our inclusion of a wide range of study designs was in recognition of the emerging nature of this body of literature, and was reflected in the findings that no studies were published between 2004 and 2008.

Importantly, any comments about the potential for effectiveness of the interventions outlined above are based on the data (both outcomes and adverse events) reported in these studies. Needless to say, safety considerations for any future studies would need to be thoroughly investigated in the first instance.

The information presented in this REA is a summary of information presented in available papers. We recommend readers source the original papers if they would like to know more about a particular intervention or study.

Conclusion

The current evidence base for hallucinogens for treatment of PTSD, anxiety, and depression is currently lacking in sufficiently high quality research to support direct recommendations. The findings of this review do, however, provide some guidance on where future research efforts could be directed should there be interest in this area. There is an opportunity for funders and researchers to consider high quality research, particularly in the areas of MDMA as an adjunctive treatment for PTSD, and cannabis as a treatment for PTSD sleep disturbance and nightmares. This kind of research, where safety concerns have been fully investigated and evaluated, may ultimately increase the range of treatments available to those who develop PTSD.

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Appendix 1

Population Intervention Comparison Outcome (PICO) framework

This question was formulated within a Population Intervention Comparison Outcome (PICO) framework. Application of a PICO framework helps to structure, contain and set the scope for the research question. Inclusion of intervention and comparison components is dependent on the question asked, and may not be appropriate for all question types.

- **What is the effectiveness of cannabis, ketamine, MDMA, LSD, psilocybin, and GHB as treatments for mental health disorders?**
    - **PICO format:** In people with PTSD, anxiety, or depression, is there evidence that illicit substances (i.e. cannabis, ketamine, MDMA, LSD, psilocybin, or GHB) that are administered as a therapeutic intervention will lead to improved mental health outcomes?

P Patient, Problem, Population	**I** Intervention	**C** Comparison (*optional*)	**O** Outcome *when defining "more effective" is not acceptable unless it describes* **how** *the intervention is more effective*
Patient – healthy adults (i.e., not suffering a life-threatening disease) with PTSD, anxiety, or depression Problem – PTSD, anxiety, or depression Population – adults	Cannabis, ketamine, methylenedioxy-methamphetamine (MDMA), lysergic acid diethylamide (LSD), psilocybin, or gamma-hydroxybutyric acid (GHB) which targets PTSD, anxiety, or depression	Any comparison	Primary outcomes: Improvements in PTSD, anxiety, or depression symptoms Secondary outcomes: Improvements in pain, quality of life

Appendix 2

Example search strategy

The following is an example of the search strategy conducted in the Embase database:

Step	Search Terms	No of records
S1	("posttraumatic stress disorder" or "post*traumatic stress" or PTSD or PTSS or "posttraumatic stress syndrome" or "post*traumatic stress syndrome" or trauma or "acute stress disorder" or ASD).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	359408
S2	limit 1 to (human and english language)	247729
S3	(depression or "major depressive disorder").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	582744
S4	limit 3 to (human and english language)	418208
S5	(anxiety or "anxiety disorder" or GAD or "generali*ed anxiety disorder").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	308897
S6	limit 5 to (human and english language)	229854
S7	(cannabidiol or cannabinoid or THC or "Cannabis extract" or "DELTA9-THC" or "DELTA9-tetrahydrocannabinol" or tetrahydrocannabinol or CBD or epidiolex).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	43181
S8	limit 7 to (human and english language)	22323
S9	(MDMA or methlenedioxymethamphetamine or "3,4-methylenedioxymethamphetamine" or ectasy or molly).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	8875
S10	limit 9 to (human and english language)	5252

S11	(LSD or "lysergic acid diethylamide" or psychedelic*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	15833
S12	limit 11 to (human and english language)	6671
S13	(GHB or "gamma-hydroxybutyrate" or "sodium oxybate" or xyrem).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	3960
S14	limit 13 to (human and english language)	2252
S15	(psilocybin or mushroom or "magic mushroom*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	17050
S16	limit 15 to (human and english language)	4417
S17	S2 or S4 or S6	745884
S18	S8 or S10 or S12 or S14 or S16	38972
S19	S17 and S18	4660
S20	(intervention or pharmacologic* or pharmacotherapeutic or treatment or medication or psychopharmacology).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	6866967
S21	limit 20 to (human and english language)	4231225
S22	S19 and S21	2541
S23	exp KETAMINE/ or ketamine.mp.	36565
S24	limit 23 to (human and english language)	17455
S25	limit 24 to (human and english language)	198
S26	S24 and S26	73
S27	S22 and S27	2614

Appendix 3

Quality and bias checklist

Chalmers Checklist for appraising the quality of studies of interventions[104]

Completed		
Yes	No	
		1. **Method of treatment assignment**
		• Correct, blinded randomisation method described OR randomised, double-blind method stated AND group similarity documented
		• Blinding and randomisation stated but method not described OR suspect technique (eg allocation by drawing from an envelope)
		• Randomisation claimed but not described and investigator not blinded
		• Randomisation not mentioned
		2. **Control of selection bias after treatment assignment**
		• Intention to treat analysis AND full follow-up
		• Intention to treat analysis AND <25% loss to follow-up
		• Analysis by treatment received only OR no mention of withdrawals
		• Analysis by treatment received AND no mention of withdrawals OR more than 25% withdrawals/loss-to-follow-up/post-randomisation exclusions
		3. **Blinding**
		• Blinding of outcome assessor AND patient and care giver (where relevant)
		• Blinding of outcome assessor OR patient and care giver (where relevant)
		• Blinding not done
		• Blinding not applicable
		4. **Outcome assessment (if blinding was not possible)**
		• All patients had standardised assessment
		• No standardised assessment OR not mentioned
		5. Additional Notes
		• Any factors that may impact upon study quality or generalisability

Appendix 4

Evidence profile: Stand-alone treatments

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Cannabis							
Cannabis for PTSD							
Cameron, Watson, & Robinson (2014)	Retrospective chart review	N = 104	I: Nabilone administered for PTSD symptoms and PTSD-related sleep disturbances C: N/A Nabilone was administered orally, as powder in water.	Nabilone dosage: -Initial dose: M = 1.4mg/day -Final dose: M = 4.0mg/day Length of time on nabilone: -M = 11.2 weeks	Canada Inmates within a Secure Treatment Unit (STU) with a variety of clinically diagnosed serious mental illness M = 32.7 years, range 19-55 years Male 100%	PTSD-related insomnia and nightmares - Insomnia (number of hours slept, sleep quality) (self-report) -Frequency of nightmares (self-report) PTSD symptoms -The PTSD Checklist – Civilian Version (PCL-C) (self-report)	Chronic pain Global Assessment of Functioning (GAF)

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[2] Mean age and SD is given when provided, alternatively age range is provided

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
This was a retrospective patient chart review examining the dosing, efficacy, and adverse effects of nabilone to treat PTSD-related insomnia and nightmares. Results indicated significant post-treatment improvements compared to pretreatment, in the following self-reported measures: (i) PTSD-associated insomnia improved with a significant increase in number of hours slept (p <0.001), (ii) PTSD-associated nightmares significantly decreased in frequency ($p < 0.001$), and (iii) PTSD symptoms were significantly reduced from 'moderate' to 'borderline-mild' (p = 0.001). Secondary outcomes were (i) subjective improvements in chronic pain reported by 89.6% of participants using nabilone for chronic pain (n = 68), and (ii) a significant improvement in the clinician-rated post-treatment GAF score (p = 0.001), which reflected a shift from 'serious' to 'moderate' impairments in functioning. Adverse effects occurred relatively more often in cannabis-naïve individuals, and overall, 31 (29.8%) participants reported adverse effects, of which 10 chose to abandon the trial. The most serious adverse effect was psychosis (n=2), and both participants who experienced this effect had pre-existing psychotic illness. Other adverse effects included sedation, dry, feeling 'stoned', orthostatic hypotension, agitation, and headache. Twenty participants abandoned the nabilone trial primarily due to adverse effects and abuse of other medications. Notably, all patients were receiving concurrent treatments with other psychotropic medication/s and a range of psychotherapies which were not controlled for in the analysis.							
Fraser (2009)	Retrospective chart review	N = 47	I: Nabilone administered for PTSD-related nightmares C: N/A Nabilone was administered orally, as capsules.	Nabilone dosage: -The commencing dose was 0.5mg daily, titrated as needed. -The average effective dose was 0.5mg/day, taken one hour before bedtime (range: 0.2mg to 4.0mg/day)	Canada Patients diagnosed with PTSD and having treatment-resistant PTSD-related nightmares M = 44 years [SD = 9] Female 57.4%	PTSD-related nightmare intensity -Self-rated Likert-type scale (1-5, with 5 being the most intense) Hours of sleep -Self-tracking sheet	Subjective reports of sleep time, sleep quality, reduction of daytime flashbacks and night sweats
This was an open-label, retrospective chart review with no control group, designed to evaluate the effects of nabilone on treatment-resistant nightmares in patients (n = 47) with PTSD. Compared to baseline, 34 (72%) of patients receiving nabilone reportedly experienced either total cessation of nightmares (n=28), or a significant reduction in nightmare intensity/severity (n = 6).							

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Improvement in sleep time and a reduction of daytime flashbacks and night sweats were subjectively noted by "some" patients (number not reported). Following four to 12 months of nabilone therapy, four (8.5%) patients were able to discontinue their existing medications (their nightmares did not return, or returned at a reduced level, and did not require medication control). The other 43 patients (91.5%) experienced a recurrence of nightmares upon nabilone withdrawal (usually within the first two nights). Nightmares were controlled again when nabilone treatment was reinitiated, and these participants were asked to attempt withdrawal every six months. This was ongoing at the time of the report, so follow-up results were not available. No adverse effects were reported, but 13 (28%) patients experienced mild-moderate side effects (including light headedness, forgetfulness, dizziness, and headache), leading to discontinuation of nabilone therapy.							
Jetly, Heber, Fraser, & Boisvert (2015)	Double-blind RCT, placebo controlled crossover design	N = 10	I: Nabilone administered for PTSD-related nightmares. Group 1: Nabilone, followed by placebo Group 2: Placebo, followed by nabilone Nabilone was administered orally, as tablets	Nabilone dosage: -The commencing dosage was 0.5mg, titrated weekly to a maximum of 3.0mg. -The dosage achieved at week five was maintained for the final two weeks of the treatment period. Each treatment period was seven weeks, and the two treatments were separated by a two-week washout period	Canada Active duty military personnel with currently diagnosed PTSD M = 43.6 years [SD = 8.2] Male 100%	PTSD-related nightmares -The CAPS Recurring and Distressing Dream Scores (clinician-administered)	- The CAPS Difficulty Falling or Staying Asleep item -Sleep diary log (total sleep time and number of awakenings per night) -The PTSD Dream Rating Scale - The Clinical Global Impression of Change (CGI-C)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Assessments were conducted at the start and end of each seven-week trial period, and no follow-up was reported. Compared to the placebo condition, the nabilone condition demonstrated significantly greater reductions in the frequency and intensity of PTSD-related nightmares ($p = 0.03$). Separating out the item scores saw a significant reduction for frequency ($p = 0.05$), but not for intensity ($p = 0.06$). At the end of the nabilone treatment period, four participants reported no distressing dreams in the last week, compared to 0 participants in the placebo condition. Additionally, four placebo participants reported daily or almost daily distressing dreams at the end of their treatment period, while no nabilone participants did. Significantly greater improvements were observed in the nabilone condition compared to the placebo condition for the secondary outcomes including: clinician rated global change (CGI-C) scores ($p = 0.05$), and general well-being (GWBQ) scores ($p = 0.04$). However, there was no effect of nabilone on sleep quality and quantity. Common side effects in the nabilone condition were dry mouth and headache, although nabilone was generally well-tolerated.							
Roitman, Mechoulam, Cooper-Kazaz, & Shalev (2014)	Open label pilot study with no control group	N = 10	I: THC administered for chronic PTSD C: N/A THC was self-administered sublingually, after being dissolved in olive oil.	THC dosage: -10mg per day (taken in two 5mg dosages) for three weeks	Jerusalem, Israel. Outpatients with chronic PTSD M = 52.3 years [SD = 8.3] Male 70.0%	PTSD symptoms -CAPS (clinician-administered)	Global improvement and sleep quality -The Clinical Global Impression Scale (CGI) -The Pittsburgh Sleep Quality Index (PSQI) -The Nightmare Frequency Questionnaire (NFQ) -The Nightmare Effects Survey (NES) [*Clinician-administered*]
Results did not demonstrate a significant reduction in total CAPS score posttreatment, however a statistically significant improvement was seen in hyperarousal symptoms ($p < .02$). Significant improvements were also identified in global symptom severity (CGI-S; $p < .02$), global symptom improvement (CGI-I; $p < .03$), PTSD-related sleep quality (PSQI; $p < .05$), and sleep disturbances							

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
(frequency of nightmares (NFQ; $p < .04$)). Despite short-term reductions in hyperarousal symptoms and PTSD-related sleep disturbances, follow-up data was not collected and therefore the long-term impact of THC could not be assessed. Of note, existing psychotropic medication use was allowable during the trial, and this was not controlled for in analyses.							
Cannabis for anxiety							
Fabre & McLendon (1981)	STUDY 1: Pre-post, open-label study, with no control group STUDY 2: Double-blind study with a placebo comparison group	STUDY 1 N = 5 STUDY 2 N = 20	I: Nabilone administered for anxiety STUDY 1: I: Nabilone (n = 5) C: N/A STUDY 2: I: Nabilone (n = 10) C: Placebo (n = 10) The method of administration of nabilone was not reported.	BOTH STUDIES: 28-day treatment period, preceded by a four-day washout period STUDY 1: Nabilone dosage: -Dosage commenced at 2mg/day (1mg twice per day), adjusted to a maximum of 10mg/day, M = 2.8mg/day (range: 2 to 8mg/day) STUDY 2: Nabilone dosage: -Fixed dose of 3mg per day (1mg three times per day)	Texas, USA BOTH STUDIES: Psychiatric outpatients suffering from psychoneurotic anxiety STUDY 1: M = 29.4 years, range 22–35 years Male 100% STUDY 2: M = 29.0 years, range 19–41 years Male 75.0%	Anxiety symptoms -Hamilton Anxiety Rating Scale (HAS) (clinician-administered)	-Patient's Global Impressions (SCL-56) -Clinical Global Impression Scale (CGI)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
These two studies trialled nabilone for the treatment of anxiety. Study 1 reported a reduction in the total HAS score, and in both factors of the HAS (somatic and psychic anxiety factors), all of which were significant at $p < 0.001$. Additionally, improvements were reported on the clinician-rated CGI-I (n = 5) and CGI-S (n = 3). Statistical tests were not conducted due to small sample size. All five participants reported side effects, and requested that their dosage be lowered when side effects occurred. Side effects were dry mouth, drowsiness, lethargy, headaches, and dry eyes. For study 2, HAS scores (somatic and psychic anxiety factors, and total score) were reported to be significantly lower posttreatment for the nabilone group compared to the placebo group ($p < 0.001$). The nabilone group demonstrated a 50% reduction in the HAS total score at day 7 which was maintained to day 32, whereas the placebo group showed "only a slight and insignificant reduction" in anxiety. Additionally, the CGI showed a greater improvement for the nabilone group compared to the placebo group ($p = 0.002$). Patient-reported depression and anxiety (SCL-56) was "greatly reduced" for the nabilone group by day 11, continuing to decline to the end of the trial (significance values were not reported). Side effects were dry mouth, dry eyes, drowsiness, headaches, and insomnia. All participants in the nabilone group (n = 10) completed the study, while five (50%) from the placebo group (n = 10) dropped out before completion of study due to lack of relief of anxiety symptoms.							
Cannabis for depression							
No studies identified							
				Ketamine			
Ketamine for PTSD							
Feder et al. (2014)	Randomised, double-blind, crossover trial	N = 41	I: Ketamine hydrochloride administered for PTSD (n = 22) C: Midazolam* (active placebo) (n = 19) Ketamine was delivered intravenously.	Ketamine hydrochloride dosage: -One dose of 0.5 mg/kg Midazolam dosage: -One dose of 0.045 mg/kg	NY, USA Patients with chronic PTSD and associated MDD Age range: 18–55 years	PTSD severity -CAPS (clinician-administered) -Impact of Event Scale–Revised (IES-R) (self-report) (assesses subjective distress	Depression -Montgomery-Asberg Depression Rating Scale (MADRS) -Quick Inventory of Depressive

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
			*Midazolam is a medication which is used for anesthesia	Ketamine and midazolam dosages were separated by two weeks.	-Ketamine: M = 36.4 [SD = 10.8] -Midazolam: M = 35.7 [SD = 10.0] Female 46.3%	caused by traumatic events)	Symptomatology Self-Report (QIDS-SR). Global Functioning -Clinical Global Impression (CGI) – Severity and – Improvement scales
This study included participants with a CAPS score of at least 50. Crossover analyses revealed significant improvements in PTSD symptom severity (IES-R) in the ketamine condition compared to placebo controls ($p < 0.05$). No residual crossover effects were identified. Comorbid depression symptoms predicted PTSD symptom severity post-infusion, with the ketamine group showing a significantly greater improvement ($p < 0.01$). Seven participants demonstrated maintained symptom reduction at seven days post-infusion, although significant group differences in mean CAPS scores were not observed. Depression symptoms post-infusion did not differ by group. Of note, multiple adverse events were recorded. Transient dissociative symptoms occurred in most participants, although manic or psychotic symptoms were not observed, One participant discontinued ketamine infusion after receiving a higher dose in error, while three participants required acute beta-blocker treatment to reduce blood pressure elevations. Frequently reported side-effects of ketamine use included blurred vision, dry mouth, fatigue, nausea/vomiting and poor coordination. Additionally, it is worth noting that fewer than 50% of participants had previously received psychotropic medication for the treatment of psychiatric conditions.							
Womble et al. (2013)	Case study	N = 1	I: Ketamine administered for MDD associated with PTSD. C: N/A Ketamine was delivered by intravenous (IV) infusion.	Ketamine dosage: -35mg (calculated as 0.5mg/kg)	Alabama, USA Combat veteran diagnosed with PTSD and chronic MDD Male, 26 years	Comorbid depression and PTSD -Subjective self-report of anxiety and depression, sleep improvement, and nightmare reduction	

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
After obtaining vital signs, the patient was administered a range of substances, beginning with oxygen by nasal cannula, followed by intravenous midazolam (3mg) as a pre-induction medication. Once an anxiolytic effect was observed, he was administered propofol (70mg) plus 30mg of lidocaine. Once a hypnotic state was achieved, a 20-minute infusion by IV piggyback was administered of propofol (30mg) and ketamine (35mg, which was 0.5mg per kg of bodyweight). No adverse effects were observed, however the patient reported difficulty focusing his vision, and of having a slight headache. Improved behaviours, such as smiling and joking, were observed before he was discharged. Follow-up self-reports were of complete resolution of anxiety and depression lasting from between one and 14 days post-infusion. He also experienced normalised and restorative sleep, and the disappearance of all debilitating nightmare events. After 14 days post-infusion however, he began to relapse into his pre-infusion state of depression.							
Ketamine for anxiety							
No studies identified							
Ketamine for depression							
Burger et al. (2016)	Proof-of-concept, randomised, double-blind trial	N = 10	I: Ketamine administered for acute suicidality (n = 3) C: Placebo (saline) (n = 7) Ketamine was delivered intravenously.	Ketamine dosage: -A single dose of 0.2mg/kg	San Diego, USA Active duty military US Marine Corp and Navy personnel who had voluntarily presented to an emergency psychiatric department for suicidality or acute depression M = 27.5 years, range 21-41 years	Suicidality -Beck Suicidality Scale (BSS) (clinician-administered)	Hopelessness -Beck Hopelessness Scale (BHS) (self-report)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
					Male 70.0%		

This pilot study trialled intravenous ketamine use primarily for suicidality in military personnel with depressive symptoms. The trial was terminated early due to inaccurate record-keeping, therefore only 10 of the initially enrolled participants (n = 18) were included in the analyses. Participants were assessed 40, 80, 120, and 240 minutes after drug administration, as well as at discharge, and at two-week follow-up. Results were presented graphically, therefore exact scores were not discernible. At the four-hour assessment, the ketamine group scored significantly lower than the placebo group on suicidality (BSS) ($p < 0.05$), however upon discharge and at follow-up, there was no difference between groups. Hopelessness (BHS) scores for the ketamine group were significantly lower than the placebo group at the four-hour assessment ($p < 0.05$) and at discharge ($p < 0.05$), but there was no difference at follow-up. Two of three (67%) participants who received ketamine experienced significant acute decreases in suicidality and hopelessness (within 40 minutes), however the controls remained unchanged during the four-hour observation. Results suggest ketamine was superior to the placebo group in reducing self-reported suicidality and hopelessness, and the effects were rapid, yet transient. No adverse effects occurred during the trial.

| Caddy et al. (2015) | Cochrane Review | 25 studies N = 1242 | Meta-analysis and review | Varied | Patients with unipolar depression | Varied | |

Utilising the Cochrane Depression, Anxiety and Neurosis Review Group's Specialised Register (CCDANCTR), data from single- or double-blind randomised controlled trials was collected to compare adult depression outcomes between glutamate receptor modulators and control conditions, including active and non-active placebo, and electroconvulsive therapy (ECT). In total, 25 studies were included in the review, of which nine refer specifically to the use of ketamine. Among the included studies, intravenous ketamine treatment was the sole glutamate receptor modulator to demonstrate efficacy above that of placebo. Higher numbers of clinical responders were noted in ketamine conditions compared to midazolam at 24 hours (OR 0.36, 95% CI 0.14 to 0.58), 72 hours (OR 0.37, 95% CI 0.16 to 0.59), and one week post-infusion (OR 0.29, 95% CI 0.08 to 0.49). However, the lasting effects of ketamine use were undetermined at two weeks post-infusion. In contrast to active and inactive placebos, ketamine elicited more confusion and emotional blunting and was perceived to be less tolerable than active placebo control (midazolam). A single study demonstrated greater symptom improvement following ketamine infusion in contrast to ECT at 24 hours (OR 28.00, 95% CI 2.07 to 379.25) and 72 hours (OR 12.25, 95% CI 1.33 to 113.06) posttreatment. However, these effects were not maintained at one or two week follow-ups. Caddy and colleagues note that long-term efficacy of glutamate receptor modulators, in particular ketamine, is unclear with limited support for symptom improvement at one to two weeks post-infusion. The authors add that the global quality of evidence is limited due to small sample sizes and risk of experimental bias. Adverse events included blood pressure and heart rate changes were noted. Further, many trials did not provide information on all pre-specified outcomes and salient issues such as suicidality, cognitive and dropout rates due to adverse effects and the intravenous nature of ketamine were infrequently acknowledged.

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Jafarinia et al. (2016)	Double blind, parallel-group RCT	N = 40	I: Ketamine administered for depression in chronic pain patients (n = 20) C: Diclofenac* (n = 20) Ketamine was delivered orally, as capsules. *Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat mild to moderate pain	Ketamine dosage: -50mg three times/day for six weeks Diclofenac dosage: -50mg three times/day for six weeks	Tehran, Iran Outpatients with chronic pain (headache) I: M = 40.7 years [SD = 8.71] C: M = 38.95 years [SD = 9.22] Female 75%	Depressive symptoms -Hamilton Depression Rating Scale (HDRS) (clinician-administered) -Hospital Anxiety and Depression Scale (HADS) – Depression scale only (self-rated)	
Score reductions in the HADS depression subscale were significantly greater in the ketamine group compared to the diclofenac group at week three (Cohen's d: 1.13, $p = 0.001$) and at week six (post-intervention; Cohen's d: 0.84, $p = 0.012$). Improvements in HDRS scores were not significantly different between treatment groups at week three. However at week six, mean HDRS score reduction in the ketamine group was significantly greater than the diclofenac group (Cohen's d: 0.79, $p = 0.017$). Response rates (where 'response' was defined as at least a 50% reduction in the HDRS score) and remission rates (where 'remission' was defined at an HDRS score of 7 or less) were not significantly different for the two treatment groups at week three, but at week six the ketamine group responded ($p = 0.008$, odds ratio for response: 8.50) and remitted ($p = 0.031$) significantly more than the diclofenac group. Furthermore, ketamine participants responded ($p = 0.002$) and remitted significantly sooner ($p = 0.013$) when compared to diclofenac participants. No serious adverse events were observed, however some participants experienced blurred vision, tremor, restlessness, nervousness, abdominal pain, and a transient loss of appetite. No follow-up beyond six weeks was reported.							
Kishimoto et al. (2016)	Meta-analysis	14 studies N = 588	Meta-analysis and review	Varied	Varied	Major depressive disorder	

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Kishimoto and colleagues (2016) meta-analysed 14 parallel-group or cross-over RCTs comparing single intravenous infusion of ketamine (9 studies, n = 234) or a non-ketamine (5 studies, n = 354) NMDA receptor antagonist versus placebo/pseudo-placebo in patients with major depressive disorder (MDD). They concluded that a single infusion of ketamine, but less so non-ketamine NMDA receptor antagonists, has ultra-rapid efficacy for MDD, lasting for up to one week. Ketamine reduced depression significantly more than placebo/pseudo-placebo beginning at 40 minutes, peaking at day 1 (Hedges' g = -1.00, 95% CI -1.25 to -0.73, p < 0.001), and losing superiority by days 10-12. Non-ketamine NMDA receptor antagonists (e.g. memantine, traxoprodil, lanicemine, and rapastinel) induced smaller effect sizes than ketamine, and were only superior to placebo/pseudo-placebo on days 5-8 (Hedges' g = -0.37, 95% CI -0.66 to -0.09, p = 0.01), however, the reasons underlying this difference remain unclear.							
Singh et al. (2016)	Double blind RCT	N = 67	I: Ketamine administered for depression (n = 35) C: Intravenous inactive placebo (0.9% sodium chloride) (n = 32) Ketamine was administered intravenously.	Ketamine dosage: -0.5mg/kg either two times/week (n = 18) or three times/week (n = 17) for four weeks	USA Outpatient population with treatment-resistant depression M = 43.9 [SD = 11.0] Female = 67%	Depression – Montgomery-Asberg Depression Rating Scale (MADRS) (clinician-administered)	Clinical Global Impressions (CGI)
Participants assigned to the ketamine condition received doses either two or three times weekly. Change to depression symptom severity (MADRS) was assessed between baseline (pre-infusion), day 15 and day 29 of treatment. Mean MADRS score from baseline to day 15 were significantly improved in both ketamine dosing groups when compared to placebo controls (p < 0.001). Mean difference in MADRS scores did not differ between ketamine frequencies. MADRS scores from baseline to day 29 showed a trend for improvement in both ketamine dosing conditions when compared to placebo controls, although significance values were not reported. Significantly higher proportions of clinical responders and remitters were identified in both ketamine dosing groups compared to placebo controls (p < 0.05). Additionally, significant decreases were observed in CGI scores for both ketamine dosing groups in contrast to placebo controls (p = 0.01). Two adverse events were noted: one patient reported significant anxiety and was subsequently hospitalised, and another patient attempted suicide on day 40 of the trial. Common treatment side-effects included headache, anxiety, nausea and dizziness. Dissociation was observed shortly after infusion and resolved within three hours post-infusion.							

Evidence profile: Adjunct treatments

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
MDMA							
MDMA for PTSD							
Bouso, Doblin, Farre, Alcazar, & Gomez-Jarabo (2008)	Double-blind RCT with placebo control	N = 6	MDMA-assisted psychotherapy (MDMA-AP) administered for PTSD I: MDMA plus psychotherapy (n = 4) C: Placebo plus psychotherapy (n = 2) The method of administration of MDMA was not reported.	Number of non-drug psychotherapy sessions: -Six (90 minutes each) – three preparatory plus three integration sessions Number of experimental drug psychotherapy sessions: -One (8 hours) MDMA dosage: -Single dose of 50mg (n=3) or 75mg (n=1)	Madrid, Spain Women with chronic, treatment-resistant PTSD secondary to a sexual assault M = 35.7 years, range: 29-49 years Female 100%	- PTSD Symptoms (SSSPTSD) (a Spanish adaptation of the PSS) -State-Trait Anxiety (STAI-S) -Depression (BDI) -The Hamilton Rating Scale (HAM-D) (clinician-administered)	Self-reported fears of sexual assault victims -The Modified Fear Scale (MFS III) Social and work-related adjustment -The Maladjustment Scale (MS) Global self-esteem -The Rosenberg Self-Esteem scale (SE/R)
This study assessed the efficacy of a single, low dose of MDMA, administered as an adjunct to psychotherapy for the treatment of chronic, treatment-resistant PTSD. The trial was terminated prematurely after treating six of the anticipated 29 participants, due to "political pressures" described as "a series of political decisions as a result of unfavourable media coverage and unrelated to any scientific or ethical considerations". Due to the small sample size, results were presented descriptively. For the placebo group, the mean pretreatment versus posttreatment score for the SSSPTSD was 44.5 and 40.0 (reduction of 4.5, or 10.1%) respectively, while for the MDMA group, these scores were 37.3 and 28.3 (reduction of 9, or 24.1%), respectively. At one-month follow-							

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[3] Mean age and SD is given when provided, alternatively age range is provided

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
up, mean SSSPTSD score for the MDMA group continued to decline to 25.0 (participants in the placebo group did not take part in the one month follow-up). Mean pretreatment and posttreatment scores for the remainder of the outcome measures were: STAI-S, (placebo: 28.5 and 28.0; MDMA: 38.6 and 25.6 (one-month follow-up = 33.0)); the BDI (placebo: 20.0 and 23.5; MDMA: 25.6 and 15.0 (one-month follow-up = 16.6)); and HAM-D (placebo: 35.5 and 22.5; MDMA 39.0 and 22.0 (one-month follow-up = 21.6)). Given the small sample size and limited placebo control condition, inferential statistics were not included. Thus, the generalisability of this study is limited to the descriptive findings of this small cohort.							
Mithoefer et al., (2011[a] & 2013)	2011: Double-blind, inactive placebo, crossover RCT 2013: Prospective long-term follow-up	N = 20	MDMA-assisted psychotherapy (MDMA-AP) administered for PTSD I: Psychotherapy[b] and MDMA (n = 12) C: Psychotherapy[b] and inactive placebo (lactose) (n = 8) MDMA was administered orally, by capsule. Follow-up: Assessments administered 17 to 74 months (M = 45.4 months, SD = 17.3] following initial study close.	Number of non-drug psychotherapy sessions: -Between two and eight introductory sessions; and -Four integration sessions after each enhanced session; and -One final integration session two months after the second enhanced session Number of experimental MDMA- or placebo-enhanced, exposure-based sessions: -Two	USA Psychotherapy patients with chronic, treatment-resistant PTSD symptoms M = 40.4 years [SD = 7.2] Female 85%	- PTSD (CAPS & IES-R)	

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
				MDMA dosage: -125mg (+ 62.5mg) prior to each of two experimental sessions			

PTSD symptom severity was assessed at baseline, four days post-intervention, and two months following the final experimental session. MDMA recipients showed a significantly greater decrease in PTSD severity (CAPS) and physical response to stress (IES-R) across post-baseline time points, when compared to placebo controls ($p < 0.01$ and $p < 0.05$ respectively). Additionally, 83% of MDMA recipients demonstrated a clinical response to the experimental condition, in contrast to 25% of the placebo condition. Clinical response was defined as a greater than 30% reduction in baseline CAPS total severity score.

In their secondary study, Mithoefer et al. (2013) collected follow-up data on posttreatment symptom outcomes, ranging from 17 to 74 months following study completion. Statistically significant differences in PTSD symptom severity (mean CAPS scores) were not observed between two months post-intervention and long term follow-up. Additionally, psychotherapy and medication management were resumed by some participants following the initial study conclusion and were not controlled for in follow-up analyses. Notably, the authors utilised independent (i.e. non-related) samples methodology to assess changes within a dependent, or related, sample.

[a]Mithoefer et al. (2011) released an addendum to their 2011 article, noting that an important reference was omitted in error.

[b]Psychotherapy modality comprised principles of LSD psychotherapy, Holotropic Breathwork and music interpretation, which have not been validated for use in populations with PTSD.

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD) Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Oehen, Traber, Widmer, & Schnyder (2013)	Double-blind, active placebo RCT	N = 12	MDMA-assisted psychotherapy (MDMA-AP) administered for PTSD I: MDMA (full dose) plus non-drug therapy sessions (n=8)	Number of non-drug psychotherapy sessions: -Twelve (two preparatory sessions and 10 integration sessions)	Switzerland Patients with chronic, treatment-refractory PTSD M = 41.4 years [SD = 11.2] Female 83.3%	- PTSD (CAPS (*German version*), PDS (German version), IES-R	

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
			C: Active placebo (low dose MDMA) plus non-drug psychotherapy sessions: (n=4) MDMA was administered orally, by capsule.	Number of experimental sessions: -Three (between eight and 10 hours each) MDMA dosages: -Full-dose: 187.5mg of MDMA in two doses (125mg plus 62.5mg supplemental) administered in each experimental session -Active placebo (low dose): 37.5mg of MDMA in two doses (25mg plus 12.5mg supplemental) administered in each experimental session	PTSD longevity: M = 18.3 years [SD = 12.0]		

Results showed no significant group differences in PTSD symptom reduction (CAPS) for MDMA compared to placebo control ($p = 0.066$). Changes in CAPS scores from pre to posttreatment were small (15.6 points decrease in the MDMA group and 3.1 points increase in the placebo group), and all participants still fulfilled PTSD diagnostic criteria at posttreatment. A significant reduction in self-reported PTSD symptoms was identified, as measured by the PDS ($p = 0.014$). Effect sizes were not reported. Three full dose recipients were classified as "non-responders" and received an additional dose. Clinical response at two months posttreatment was observed in four of the eight full-dose group, although all participants continued to meet criteria for PTSD diagnosis. At 12-month follow-up (n = 11), five participants no longer met diagnostic criteria for PTSD and a broad trend toward CAPS score improvement was identified. Psychotropic medication use and external psychotherapy were resumed posttreatment, and were not controlled for in follow-up analyses. No drug-related serious adverse events occurred, although some participants reported moderate insomnia, loss of appetite, headache, dizziness, impaired balance, difficulty concentrating, and anxiety.

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Oehen et al. (2013) utilised a similar study design and an identical treatment protocol to those used in the Mithoefer et al. (2011) RCT. However, in contrast to Mithoefer and colleagues, the results of this study did not replicate the favourability of MDMA treatment over placebo control for PTSD symptom reduction. The study authors attribute this discrepancy to differing sample characteristics, rater and therapist differences, and chance.							
MDMA for anxiety							
No studies identified							
MDMA for depression							
No studies identified							
LSD							
LSD for PTSD							
No studies identified							
LSD for anxiety							
Gasser et al., (2014)	Phase 2 pilot study, double-blind RCT with active placebo	N = 11	LSD-assisted psychotherapy for anxiety I: LSD experimental group (n = 8) C: Active placebo group (n = 3) LSD was administered orally, as free base in capsules.	Number of sessions: -Two experimental sessions (LSD or placebo) two to three weeks apart, plus six psychotherapy sessions LSD dosage: -Experimental 200 μg	Switzerland Patients diagnosed with anxiety associated with life-threatening illnesses. Male 63.6% M = 51.7 years [SD = 9.1]	- Anxiety (STAI)	- Quality of Life (European Cancer Quality of Life Questionnaire) -The SCL-90-R - Anxiety and Depression (HADS)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
				-Active placebo 20 µg; after two-month follow up, all (n = 3) crossed over to receive 200 µg dosage			

To be included, participants were required to have a STAI score greater than 40 on either the state or trait subscale. A significant visit x group interaction was identified for trait anxiety ($p < 0.05$, Cohen's $d = 1.1$); of those in the experimental condition, three of eight showed reductions in trait anxiety below threshold, while all active placebo participants reported increased trait anxiety. No significant differences were observed between two- and 12-month follow-up scores for trait anxiety in those receiving LSD doses (n = 9), suggesting sustained benefits over time. Similarly, a significant visit x group interaction was identified for state anxiety ($p < 0.05$, Cohen's $d = 1.2$), with three of eight in the experimental condition showing reductions below threshold, while two of three controls reported increased state anxiety. These results were maintained at 12-month follow-up for those receiving experimental LSD doses. No severe adverse events were reported, although commonly reported side effects of active LSD treatment included emotional distress, feeling cold, gait disturbance, and illusions.

| McCabe, Savage, Kurland, & Unger (1972) | RCT | N = 85 | LSD-assisted psychotherapy (psychedelic therapy) for the treatment of neurotic disorders, including anxiety and depression. Group I: Conventional treatment (group therapy only) (n = 27) Group II: Psychedelic therapy - Low-dose LSD control group (n = 30) | Non-drug group therapy (Group I only): -Three sessions per week in groups of between three and eight; conducted over three to five weeks. Mean hours of formal therapy was 21.2 Psychedelic therapy (Groups II and III): | USA Hospital inpatients with a psychoneurotic diagnosis. Clinically, the patients were depressed, anxious, and typically received a "depressive reaction" diagnosis M = 32.9 years, range 19–53 years | Neuroticism, with anxious and depressive features (MMPI) | - Other personality measures (The Eysenck Personality Inventory, The Personal Orientation Inventory |

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
			Group III: Psychedelic therapy - High-dose LSD experimental group (n = 28) The method of administration of LSD was not reported, other than being referred to as a "drug preparation".	-Preparation period - Mean hours of formal therapy was 19.4 (Group II), and 20.4 (Group III), conducted over three to five weeks; and -One LSD session of 12-14 hours LSD dosages: -Low dose: 50 µg -High dose: 350 µg	Female 65%		
Participants were inpatients diagnosed with "neurotic disorder" between the ages of 18 and 55. Patients presented as anxious and depressed, and typically received a "depressive reaction" diagnosis. The MMPI was administered pre- and post-treatment (conducted 5 to 7 days after treatment). Post-treatment MMPI depression scores differed significantly between the high-dose LSD group and those receiving conventional group therapy ($p = 0.039$). Significant differences were also identified in post-treatment MMPI anxiety scale scores between the conventional therapy group and both the low-dose and high-dose LSD groups ($p = 0.004$). There were no differences between high- and low-dose psychedelic therapy groups. Of note, this trial did not include a no-treatment control group.							
Richards, Grof, Goodman, &	Pilot study, pre/post	N = 31	I: LSD-assisted psychotherapy administered for anxiety and	Non-drug psychotherapy sessions:	USA Patients with cancer	Anxiety and depression -Observer* ratings using a specially	- Psychological isolation

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Kurland (1972)[a]	design with no control group		depression associated with having a life-threatening illness C: N/A LSD was administered intramuscularly.	-Preparatory sessions (M = 9.75 hours over two to three weeks); and -"Several subsequent" integration sessions LSD sessions: -28 participants received one LSD session, and three participants received 2, 4, and 6 sessions respectively over several months LSD dosage: -One dosage of between 200 and 500 µg (M = 323 µg)	M = 54.74 years, range 35-81 years Female 74.2%	developed rating scale with a range of values from -6 to +6 reflecting degree of depression and anxiety *Raters included physicians, nurses, family members, therapists, and an independent psychiatric social worker.	- Difficulty in medical management - Fear of death - Preoccupation with pain - Denial of the imminence of death

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Treatment effectiveness was assessed using pre- and post-session observer ratings and changes in narcotic administration. Ratings were made one day before and three days after LSD treatment. Pooled and averaged ratings suggest significant reductions in depression ($p < 0.01$) and anxiety ($p < 0.01$); depression pre (-3.05) and posttreatment (+0.43); anxiety pre (-2.94), posttreatment (+0.33). A trend toward significant reductions in narcotic use was also observed. [a]A secondary paper also reported on this study the following year (Grof, Goodman, Richards, & Kurland, 1973). Using the global rating scale as a marker of therapeutic success, nine patients demonstrated "dramatic" improvement following psychedelic treatment, 13 patients demonstrated "moderate" improvements, while seven patients remained symptomatically "unchanged". Additionally, two patients exhibited an increase in symptomology from pre to posttreatment.							
LSD for depression							
McCabe, Savage, Kurland, & Unger (1972)	RCT	N = 85	LSD-assisted psychotherapy (psychedelic therapy) for the treatment of neurotic disorders, including anxiety and depression.	This study reported on combined anxiety/depression outcomes. Refer to the section 'LSD for anxiety' above.			
Richards, Grof, Goodman, & Kurland (1972)[a]	Pilot study, pre/post design with no control group	N = 31	LSD-assisted psychotherapy administered for anxiety and depression associated with having a life-threatening illness .	This study reported on combined anxiety/depression outcomes. Refer to the section 'LSD for anxiety' above.			

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
[a]A secondary paper also reported on this study the following year (Grof, Goodman, Richards, & Kurland, 1973).							
Psilocybin							
Psilocybin for PTSD							
No studies identified							
Psilocybin for anxiety							
Moreno, Wiegand, Taitano, & Delgado (2006)	Modified double-blind exploratory study	N = 9	I: Psilocybin for OCD C: N/A Psilocybin was administered orally.	Psilocybin dosage: -Up to four single-dose exposures per person -Very low dose (VLD) = 25 µg/kg (n = 7) -Low dose (LD) = 100 µg/kg (n = 9) -Medium dose (MD) = 200 µg/kg (n = 7) -High dose (HD) = 300 µg/kg (n = 6) Dose escalation protocol: Each participant received dosages in the order of	USA Patients with treatment resistant OCD M = 40.9 years [SD = 13.2] Male 77.8%	OCD symptoms (Yale-Brown Obsessive Compulsive Scale (YBOCS) (self-report) Overall obsessive compulsive symptom severity -Visual analogue scale (VAS) (self-report)	Hallucinogen experience -The Hallucinogen Rating Scale (HRS) (self-report)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
				LD, MD, and HD, with VLD inserted randomly at any time after the LD			
The YBOCS and VAS were administered immediately before psilocybin ingestion (baseline) and at four, eight, and 24 hours post-ingestion while the HRS was administered at eight hours post-ingestion. Decreases in OCD symptoms, as measured by the YBOCS, were observed in all participants during one or more sessions (23% - 100% reduction in YBOCS score). A significant contrast comparison of baseline versus post-ingestion OCD symptoms was identified across all doses (YBOCS; p = .028). Although this study reports only a transient reduction of OCD symptoms, one participant achieved long-term remission at the end of the four test sessions, as measured at six month follow-up. No significant correlations were identified between HRS total and changes in OCD severity. Other than transient hypertension without relation to anxiety or somatic symptoms (n = 1), no other significant adverse effects were observed.							
Griffiths et al. (2016)	Double-blind RCT cross-over design with placebo control	N = 51	Psilocybin for anxiety and depression associated with having a life-threatening disease I: High dose psilocybin group: -High dose (n = 26) followed by low dose (n = 25) C: Very low (placebo-like) dose group: -Low dose (n = 25) followed by high dose (n = 24)	Number of treatment sessions per person: -Two sessions, spaced five weeks apart Psilocybin dosage: -High dose: The first participant received 30mg/70kg, and the remainder (n = 49) received 22mg/70kg -Very low dose: The first 12 participants	Maryland, USA Psychologically distressed cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. M = 56.3 years [SD = 1.4] Male 51%	- Anxiety and depression (GRID-HAMD-17; HAM-A; SIGH-A; BDI; HADS; (STAI) -Profile of Mood States (POMS) (self-report)	Subjective drug effect measures -Hallucinogen Rating Scale (HRS); 5-Dimension Altered States of Consciousness (5D-ASC); Mysticism Scale; States of Consciousness Questionnaire (SOCQ) Psychiatric symptoms -Brief Symptom Inventory (BSI)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
			Psilocybin was administered orally	received 3mg/70kg, and the remainder (n = 38) received 1mg/70kg			Other secondary measures: Quality of life and life meaning, optimism, death anxiety, and spirituality
At post-session assessment (five weeks after session one), participants who received the high dose prior to the low dose demonstrated significant decreases in anxiety and depression, when compared to the low dose first condition. Specifically, 92% and 60% of the high-dose first group experienced a clinically significant response and symptom remission for depression, respectively (GRID-HAMD-17; $p < 0.05$). Both of these percentages were significantly greater than those reported in the low-dose first group ($p < 0.01$), which were 32% and 16%, respectively. Similarly, 76% and 52% of the high-dose first group experienced a clinically significant response and symptom remission for anxiety, respectively (HAM-A; $p < 0.05$). Both of these percentages were significantly greater than those reported in the low-dose first group ($p < 0.01$), which were 24% and 12%, respectively. Significant differences between high dose first and low dose first groups were not identified in these domains following session two, after both groups had received high doses of psilocybin. Additionally, no significant differences were observed in response and remission rates between session two and six month follow-up, suggesting relatively sustained symptom improvement. No severe adverse events were reported, however side effects of psilocybin doses included increased blood pressure and pulse, nausea, vomiting, transient anxiety and psychotic symptoms.							
Grob et al. (2011)	Double-blind, placebo controlled pilot study.	N = 12	I: Psilocybin for anxiety and depression associated with having a life-threatening illness. C: Placebo (Niacin). Participants acted as their own control and received both conditions.	Each participant received two experimental treatment sessions. Dosages: -Psilocybin: 0.2mg/kg -Niacin: 250mg	USA Advanced stage cancer patients with anxiety and/or acute stress disorder.	- Anxiety (STAI) - Depression (BDI) -Profile of Mood States (POMS) (self-report)	Psychiatric Symptoms -Brief Psychiatric Rating Scale Consciousness -5-Dimension Altered States of Consciousness Profile

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
			Psilocybin was delivered orally.				
Broadly, trends approaching significance were observed on measures of depression and anxiety in the psilocybin condition compared with placebo controls. Observable changes in depression symptoms were not noted pre- and post-psilocybin administration. However, self-reported depression severity decreased by almost 30% between session one and 1-month follow up (BDI; $p = 0.05$), a decrease that was sustained at six-month follow-up ($p = 0.03$). Significant changes in anxiety level were not observed at two weeks post-treatment. However, self-reported trait anxiety (STAI) was significantly decreased at one-month ($p = 0.001$) and 3-month follow up ($p = 0.03$). Psychiatric symptoms did not vary between experimental and control conditions, although marked differences in state of consciousness were observed between psilocybin and niacin administrations.							
Ross et al. (2016)	Double-blind RCT, placebo controlled, crossover design	N = 29	Psilocybin-assisted psychotherapy for anxiety and depression associated with having a life-threatening illness I: Psilocybin first, followed by niacin (n = 14) C: Niacin first, followed by psilocybin (n = 15) Psilocybin was delivered orally, by capsules.	Each participant received two dosing sessions. Treatment cross-over occurred at seven weeks post-session one. Psychotherapy: -Three preparatory and three integration sessions following each dosing session Dosages: -Psilocybin – a single 0.3mg/kg dose -Niacin – a single 250mg dose	NY, USA Patients with life-threatening cancer, and cancer-related, clinically significant anxiety and depression M = 56.28 years [SD = 12.93] Female 62.1%	- Anxiety and depression (HADS; BDI; STAI) -The Profile of Mood States (POMS) (self-report) -The Brief Symptom Inventory (BSI) (self-report)	Subjective drug effects and mystical experience -The Mystical Experience Questionnaire (MEQ 30) -The Hallucinogen Rating Scale (HRS) -The 5 Dimension Altered States of Consciousness Profile (5D-ASC) Persisting effects of psilocybin -The Persisting Effects Questionnaire (PEQ)
Prior to crossover, significant differences were observed in anxiety and depression symptoms for the psilocybin group verses the control condition. Specifically, significant differences were observed in clinical response and remission rates for self-reported depression (BDI; $p < 0.01$) and anxiety (HADS-A; $p < 0.01$) symptoms at seven weeks post-session one. Significant group							

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
differences were not observed for the clinician administered measure of depression symptom changes (HADS-D). Within-group anxiety and depression reductions for the psilocybin first group were significant across all time points (baseline to each post-baseline time point), including eight month follow-up. At six month follow-up, 60 – 80% of all participants maintained clinical reductions in depression and/or anxiety. Participants' mystical or spiritual experiences (measured using MEQ 30) were highly correlated with clinical improvements and mediated a significant proportion of the treatment effects of psilocybin on depression and anxiety measures. Although severe adverse events were not recorded, symptoms including increased blood pressure, nausea, vomiting, anxiety and psychotic symptoms were reported.							
Psilocybin for depression							
Carhart-Harris et al. (2016)	Open-label, feasibility (pilot) study with no control group	N = 12	I: Psilocybin plus psychological support for depression (n = 12) C: N/A Psilocybin was delivered orally, via capsules	Psilocybin dosage: -Doses were administered in two separate sessions, seven days apart. -The first session was low-dose (10mg). -The second session was high-dose (25mg). Psychological support using a non-directive, supportive approach was provided during dosing.	London, UK Patients with moderate to severe unipolar treatment-resistant major depression (mean duration of depression 17.8 years, SD = 8). M = 42.7 years, range 30-64 years Male 50%	Depressive symptoms and severity (QIDS; BDI) (self-report) -Snaith-Hamilton Pleasure Scale (SHAPS) (self-report) -The 21-item Hamilton Depression Rating Scale (HAM-D) (clinician-rated) -Montgomery-Asberg Depression Rating Scale (MADRS) (clinician-rated)	Clinician assessment of global functioning -Global Assessment of Functioning (GAF) Additional patient-rated scales -State-Trait Anxiety Inventory (trait version only) (STAI-T) -Patient-rated subjective intensity of psilocybin's effects reported on a 0-1 scale (a feasibility measure)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Mean self-rated intensity of psilocybin experience (on a 0-1 scale) was 0.51 [SD = 0.36] for the low-dose (10mg) session, and 0.75 [SD = 0.27] for the high-dose (25mg) session. Relative to baseline, significant reductions were reported in mean QIDS scores at week one ($p = 0.002$), week two ($p = 0.002$), week three ($p = 0.002$), week five ($p = 0.003$), and three months ($p = 0.003$) after the high-dose sessions. The greatest reduction occurred at week two, and significant reductions were maintained at the end of three months. There were also significant reductions in depressive symptoms measured using the BMI at week one ($p = 0.002$), and at three months ($p = 0.002$), compared to baseline. Remission of depressive symptoms, as indicated by a score of nine or less on the BDI, was achieved by eight (67%) patients at week one, five (42%) of whom remained in remission at three months. Anhedonia was also significantly reduced at week one (SHAPS; $p = 0.002$), and at three months (SHAPS; $p = 0.002$), compared to baseline. Clinician assessments (HADS and MADRS) were conducted at week one and showed significant improvements at that time. Adverse events included transient anxiety during drug onset, transient confusion or thought disorder, nausea, headache, and mild paranoia.							
Griffiths et al. (2016)	Double-blind RCT cross-over design with placebo control	N = 51	Psilocybin for anxiety and depression associated with having a life-threatening disease	This study reported on combined anxiety/depression outcomes. Refer to the section 'psilocybin for anxiety' above.			
Grob et al. (2011)	Double-blind, placebo controlled pilot study.	N = 12	Psilocybin for anxiety and depression associated with having a life-threatening illness.	This study reported on combined anxiety/depression outcomes. Refer to the section 'psilocybin for anxiety' above.			
Ross et al. (2016)	Double-blind RCT, placebo controlled,	N = 29	Psilocybin-assisted psychotherapy for anxiety and	This study reported on combined anxiety/depression outcomes. Refer to the section 'psilocybin for anxiety' above.			

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[3] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
	crossover design		depression associated with having a life-threatening illness				
Gamma-Hydroxybutyric Acid (GHB)							
GHB for PTSD							
No studies identified							
GHB for anxiety							
No studies identified							
GHB for depression							
No studies identified							

Appendix 5

Evaluation of the evidence

Type of Intervention	Included Studies
Supported	
	None
Promising	
Ketamine for depression	- Burger et al. (2016)[8] - Caddy et al. (2015)[39] (meta-analysis) - Jafarinia et al. (2016)[97] - Kishimoto et al. (2016)[95] (meta-analysis) - Singh et al. (2016)[96]
Unknown	
Cannabis for PTSD	- Cameron, Watson, & Robinson (2014)[16] - Fraser (2009)[93] - Jetly, Heber, Fraser, & Boisvert (2015)[18] - Roitman, Mechoulam, Cooper-Kazaz, & Shalev (2014)[92]
Cannabis for anxiety	Fabre & McLendon (1981)[17]
Ketamine for PTSD	- Feder et al. (2014)[36] - Womble (2013)[94]
MDMA for PTSD	- Bouso, Doblin, Farre, Alcazar, & Gomez-Jarabo (2008)[98] - Mithoefer, Wagner, Mithoefer, Jerome, & Doblin (2011)[43] - Mithoefer et al. (2013)[99] - Oehen, Traber, Widmer, & Schnyder (2013)[9]
LSD for anxiety	- Gasser et al. (2014)[58] - Grof, Goodman, Richards, & Kurland (1973)*[102] - McCabe, Savage, Kurland, & Unger (1972)*[100] - Richards, Grof, Goodman, & Kurland (1972)*[101]
LSD for depression	- Grof, Goodman, Richards, & Kurland (1973)*[102] - McCabe, Savage, Kurland, & Unger (1972)*[100] - Richards, Grof, Goodman, & Kurland (1972)*[101]

Psilocybin for anxiety	• Moreno, Wiegand, Taitano, & Delgado (2006)[67] • Griffiths et al. (2016)*[103] • Grob et al. (2011)*[72] • Ross et al. (2016)*[75]
Psilocybin for depression	• Carhart-Harris et al. (2016)[69] • Griffiths et al. (2016)*[103] • Grob et al. (2011)*[72] • Ross et al. (2016)*[75]

*Study outcomes were for more than one disorder, therefore the study appears in more than one type of intervention