Evidence Compass

Summary Report

Hallucinogens as treatments for PTSD, anxiety, and depression

November 2017

Summary of the Rapid Evidence Assessment

Disclaimer

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This project utilised a rapid evidence assessment (REA) methodology. An REA streamlines traditional systematic review methods in order to synthesise evidence within a shortened timeframe. The advantage of an REA is that rigorous methods for locating, appraising and synthesising evidence from previous studies can be upheld. Also, the studies reported can be at the same level of detail that characterise systematic reviews, and results can be produced in substantially less time than required for a full systematic review. Limitations of an REA mostly arise from the restricted time period, resulting in the omission of literature such as unpublished pilot studies, difficult-to-obtain material and/or non-English language studies. A major strength, however, is that an REA can inform policy and decision makers more efficiently by synthesising the evidence in a particular area within a relatively short space of time and at less cost.

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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were excluded if the full text was unavailable, if the drug was not investigated as a treatment, if the paper was not peer-reviewed, if the primary outcome measure were not the focus of the review (i.e. PTSD, anxiety and depression), if they did not concern the population of interest (i.e.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. 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:
    - the evidence for cannabis in treating PTSD received an 'Unknown' ranking
    - the evidence for cannabis in treating anxiety received an 'Unknown' ranking
    - there was no evidence for cannabis in treating depression
    - the evidence for ketamine in treating PTSD received an 'Unknown' ranking
    - there was no evidence for ketamine in treating anxiety
    - the evidence for ketamine in treating depression received a 'Promising' ranking.
- The key findings for adjunct treatments were that:
    - the evidence for MDMA in treating PTSD received an 'Unknown' ranking
    - there was no evidence for MDMA in treating anxiety
    - there was no evidence for MDMA in treating depression
    - there was no evidence for LSD in treating PTSD
    - the evidence for LSD in treating anxiety received an 'Unknown' ranking
    - the evidence for LSD in treating depression received an 'Unknown' ranking
    - there was no evidence for psilocybin in treating PTSD
    - the evidence for psilocybin in treating anxiety received an 'Unknown' ranking

  - the evidence for psilocybin in treating depression received an ‘Unknown’ ranking
  - 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.

Background

Clinical research investigating the therapeutical 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.[1] 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. Hallucinogens may be considered as stand-alone or adjunctive treatments for PTSD, anxiety, and/or depression in cases of treatment-resistance or where acute symptom reduction is warranted, for example suicidality, due to the rapid effect of some hallucinogens. Additionally, some hallucinogens have been shown to strengthen the therapeutic alliance through their prosocial effects, thus enhancing the therapeutic process itself. Therefore, hallucinogens are worthy of enquiry as a possible adjunct to standard treatment approaches, as there is the need for novel pharmacological treatments that can augment psychotherapy.[2]

The aim of this REA is to examine the scientific literature for evidence of effectiveness of cannabis, ketamine, MDMA, LSD, psilocybin, and GHB as treatment for adult populations with PTSD, anxiety, or depression diagnoses or symptoms. 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 are discussed in the review.

Hallucinogens

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.[3] Hallucinogens primarily act to alter cognition and perception, which is experienced by users as an alteration to ordinary conscious experience.[4] In the current review, hallucinogens are considered as treatments for PTSD, anxiety, and depression. The hallucinogens investigated in this review are cannabis, ketamine, 3,4-methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), psilocybin, and gamma-hydroxybutyric acid (GHB).

Cannabis – Psychoactive components of cannabis (marijuana), otherwise known as cannabinoids, have been investigated as a stand-alone treatment for anxiety and PTSD-related nightmares, however its potential use for treating depression is currently largely theoretical. Cannabis acts on the endocannabinoid (eCB) system and on the fear and emotion structures of the brain which are areas that are implicated in PTSD and anxiety. It is broadly via these mechanisms that symptom reduction is thought to occur. Users of cannabis may be at risk of acute side effects, including dry mouth, dry eyes, headache, orthostatic hypotension, agitation and sedation.[5-7] Additionally, longer term cannabis use can lead to adverse psychiatric effects, for example the development of schizophrenia, particularly in adolescents, memory and cognition impairments, and impulsivity and sucicidality.[8] Long-term use is also associated with increased risk of addiction.[9]

Ketamine – Ketamine was originally developed as a general anaesthetic in 1962, and soon thereafter became a recreational drug of abuse because of its psychedelic properties.[10] More recently it has received attention as a potential stand-alone treatment for PTSD and depression, based largely on its actions on the glutamatergic system, and on brain structures implicated in the disorders. Despite its safety profile, which makes ketamine an important medicine in anaesthesia and pain management[11], there are acute and chronic risks associated with ketamine use. These include acute events such as ketamine poisoning, cardiac events, or death from overdose, and chronic physical harm such as ketamine-induced ulcerative cystitis, kidney dysfunction, and ‘k-cramps’ (intense abdominal pain).[11] Long-term use may also lead to adverse psychiatric outcomes including increased depression, impairments in memory and the ability to plan, neurological changes, and addiction.[11]

MDMA – MDMA, the main component of the drug 'ecstasy', is a synthetic compound that alters mood and perception, and induces a brief experience that is typically characterised by euphoria, increased well-being, sociability, self-confidence, and extroversion. MDMA users report having decreased feelings of fear while maintaining a clear-headed and alert state of consciousness.[12] Uncontrolled use of MDMA is associated with physical risks including hyperthermia, hyponatremia, the serotonin syndrome (confusion, difficulty walking, muscle jerks, and poor control of heart rate and blood pressure), cardiac complications, liver abnormalities, and neurological complications.[13] Psychological risks of MDMA use include depression, memory problems, anxiety, mood fluctuation, and poor concentration.[14] 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. MDMA has been investigated as an adjunct to psychotherapy for the treatment of PTSD.

LSD - LSD, also known as 'acid', is a semisynthetic drug which alters the functioning of the serotonergic system. The serotonergic system is implicated in anxiety and depressive disorders, and LSD has been trialled as a treatment for both disorders.[15] Like MDMA, LSD is used as an adjunct to psychotherapy. 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".[16] Undesired acute effects of LSD include incidence of negative mood qualities, anxiety, intense feelings of inferiority, guilt, aggressive feelings, panic, a profound fear of death, and suicidal ideation.[17] Relatively less is known about the chronic effects of LSD[18], although it is not considered to be an addictive compound.[19] One possible long-term consequence, which is applicable to all hallucinogens, is hallucinogen persisting perception disorder (HPPD).[20] Additionally, long-term LSD use has been associated with increased risk of mental illness including schizophrenia and depression.[19,21]

Psilocybin - Psilocybin occurs naturally in some species of mushroom which are commonly referred to as 'magic mushrooms'.[22] 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.[23] Psilocybin acts on the serotonergic system[24] to exert a psychedelic effect. Psychedelic experiences have been associated with sustained increases in wellbeing and optimism[25] and reduced anxious, depressive, and obsessive-compulsive symptoms.[22,26] Despite its very low physiological toxicity, long-term psilocybin use can produce adverse psychological reactions including spontaneous alterations of consciousness and flashbacks, and negative changes in psychological well-being and/or mental functions including concentration problems, mood swings, memory problems, and

being pensive and introverted.[27,28] Other potential, but rare, prolonged adverse reactions include persisting psychosis or depression.[28] Psilocybin has been trialled as an adjunct to psychotherapy and also alongside supportive, non-directive psychological support.

GHB - GHB was formerly used as a hypnotic and anaesthetic agent.[29] 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.[30] 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.

Evaluating the evidence

Assessment of the evidence was based on the following criteria:

- the **strength of the evidence base** which incorporated the quality and risk of bias, quantity of the evidence (number of studies), and level of the evidence (study design)
- the **direction** of the evidence (whether positive or negative results have been found)
- the **consistency** across studies
- the **generalisability** of the studies to the target population
- the **applicability** to an Australian context.

Ranking the evidence

Twenty-five studies met the inclusion criteria for the current review. After the evidence was evaluated, the studies were ranked as follows:

SUPPORTED	PROMISING	UNKNOWN	NOT SUPPORTED
	Ketamine for depression	Cannabis for PTSD Cannabis for anxiety Ketamine for PTSD MDMA for PTSD LSD for anxiety LSD for depression Psilocybin for anxiety Psilocybin for depression	

'**Supported**' means there was clear and consistent evidence of a beneficial effect of the intervention; '**Promising**' means the evidence was suggestive of beneficial effect, but requires confirmation with additional evidence/research; '**Unknown**' is defined as insufficient evidence at present on whether or not to support the use of this intervention, or additional evidence is required to determine efficacy of intervention; **'Not supported'** is defined as evidence suggesting that the intervention does not have an effect, or produces a harmful effect when implemented.

Implications for policy makers and service delivery

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, which are discussed below.

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, reporting 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.[8,9]

The evidence for MDMA suggested that this drug may warrant further research and examination for the treatment of PTSD. Studies involving MDMA-assisted psychotherapy 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.[13,14] These studies also raise questions for future studies. Specifically, given that 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 focused and evidence-based gold standard PTSD treatments such as prolonged exposure or cognitive processing therapy as the adjunct in the context of MDMA administration.

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-related 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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