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Efficacy of Psychoactive Drugs for the Treatment of Posttraumatic Stress Disorder: A Systematic Review of MDMA, Ketamine, LSD and Psilocybin

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ABSTRACT

The aim of this systematic review was to examine the efficacy of MDMA, ketamine, LSD, and psilocybin for the treatment of posttraumatic stress disorder (PTSD). A search of four databases for English language, peer-reviewed literature published from inception to 18th October 2019 yielded 2,959 records, 34 of which were screened on full-text. Observational studies and RCTs which tested the efficacy of MDMA, ketamine, LSD, or psilocybin for reducing PTSD symptoms in adults, and reported changes to PTSD diagnosis or symptomatology, were included. Nine trials (five ketamine and four MDMA) met inclusion criteria. Trials were rated on a quality and bias checklist and GRADE was used to rank the evidence. The evidence for ketamine as a stand-alone treatment for comorbid PTSD and depression was ranked "very low", and the evidence for ketamine in combination with psychotherapy as a PTSD treatment was ranked "low". The evidence for MDMA in combination with psychotherapy as a PTSD treatment was ranked "moderate".

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KEYWORDS
Posttraumatic stress disorder; MDMA; ketamine; psilocybin; LSD

Introduction

Current treatment guidelines for posttraumatic stress disorder (PTSD) support the use of trauma-focused Cognitive Behavioral Therapy (TF-CBT) and Eye Movement Desensitization and Reprocessing (EMDR) as first-line treatments (American Psychological Association 2017; Australian Centre for Posttraumatic Mental Health 2013). Yet PTSD remains difficult to treat, and non-response rates are high, with up to two-thirds of people failing to respond to first-line interventions (Steenkamp et al. 2015). Non-response may result from the impact of trauma on a person's ability to form trusting interpersonal relationships, which can subsequently affect the working alliance between the patient and therapist (Doukas et al. 2014). Access to first-line treatments can also be a challenge with the majority of mental health clinicians not using these interventions to treat PTSD, even when they have received requisite clinical training (van Minnen, Hendriks, and Olff 2010). For certain individuals, such as those having difficulty accessing and verbalizing traumatic memories, some first-line treatments may be unsuitable (Wild and Gur 2008). Resultantly, there remains a clear need for continued investigation of new or combination treatments for PTSD (Metcalf et al. 2019).

Recently, there has been a resurgence of interest in the potential therapeutic value of drugs with hallucinogenic or psychedelic properties in the treatment of psychiatric disorders (Garcia-Romeu, Kersgaard, and Addy 2016). *Ketamine* was developed as a general anesthetic and subsequently also became a recreational drug of abuse on account of its psychedelic and hallucinogenic properties (Jansen 2000). Ketamine acts primarily on the glutamatergic system (Vollenweider and Kometer 2010), which has been implicated in the formation of traumatic memory, mediation of the stress response, and pathophysiology of PTSD (Feder et al. 2014). While the biological mechanisms responsible for its effects on PTSD symptoms remain unclear, animal studies have shown that chronic stress reduces synaptic density and complexity in the pre-frontal cortex and hippocampus, with reversal of this following ketamine treatment (Li et al. 2011).

3,4-methylenedioxymethamphetamine (MDMA) is a synthetic compound and is typically the main constituent of the recreational drug "ecstasy". MDMA can be administered clinically and induce unique changes in human emotion (Bedi, Hyman, and de Wit 2010). When MDMA is used in combination with psychotherapy typical effects are said to include an increased ability to access and process painful or negative emotions and increase the range of positive emotions toward self and others (Mithoefer et al. 2017). The

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psychopharmacological effects of MDMA include release of monoamine neurotransmitters (Feduccia and Mithoefer 2018), resulting in temporary changes to cognition, mood & perception. MDMA also has an impact on the body via the release of cortisol, oxytocin, prolactin and vasopressin (Baumeister et al. 2014; Carhart-Harris et al. 2015; Feduccia and Mithoefer 2018).

MDMA's specific release of serotonin appears to result in a bilateral reduction of the amygdala (Carhart-Harris et al. 2015; Gamma et al. 2000), a brain structure involved in the acquisition and storage of fearful memories that is also implicated in the neurocircuitry model of PTSD (Rauch et al. 1998). The reduction of activity within the amygdala coupled with increased activation of the serotonergic system has been found to alter emotional and cognitive processes by increasing cognitive flexibility (Wagner et al. 2019), diminishing responses to negative stimuli, enhancing responses to positive emotions, and positively affecting behavior and perceptions during social interactions (Bedi et al. 2009; Wardle and de Wit 2014). Given these effects, the use of MDMA within a controlled psychotherapy environment may prove beneficial for patients with PTSD. Specifically, it is theorized that MDMA-assisted therapy could result in a mismatch between the positive emotions that patients are likely to experience whilst on the drug and within the therapeutic setting, versus the recall of traumatic memory that has previous associations with negative emotions. This mismatch could potentially lead to updating of traumatic memories (Nader, Schafe, and Le Doux 2000; Sevenster, Beckers, and Kindt 2013) which in turn can lead to reduced PTSD symptoms and fear extinction (Feduccia and Mithoefer 2018). MDMA acts as a catalyst to therapy by reducing the fear response associated with trauma memories (Mithoefer, Grob, and Brewerton 2016).

Lysergic acid diethylamide (*LSD)* is a semisynthetic serotonergic hallucinogen (Geyer, Nichols, and Vollenweider 2009). LSD produces psychosensory changes, intensified affect, and altered cognition, sometimes associated with novel or broadened interpretations of self, relationships and objects (Gasser et al. 2014). As is the case with MDMA, it is hypothesized that LSD may yield therapeutic benefit through elevating prosocial behavior, thereby enhancing therapeutic alliance and increasing the efficacy of talk-therapy (Gasser et al. 2014). It may also engender a sense of catharsis and relaxation which is helpful for working through and integrating difficult feelings and situations (Grof 1975).

4-phosphorloxy-N,N-dimethyltryptamine (Psilocybin) is a naturally occurring ingredient in certain species of mushrooms, otherwise known as "magic mushrooms" (Moreno et al. 2006). Like LSD, psilocybin acts on the serotonergic system after it is metabolized to psilocin (Carhart-Harris et al. 2016). Its psychedelic properties are attributed to its action as an agonist at serotonin 5-HT_{2A} receptors (Aghajanian and Marek 1999), and is comparative to the effects of LSD, producing increases in optimism and wellbeing and reducing negative mood (Grob et al. 2011), enhanced ability for introspection and perceptual changes which typically last 3–6 h (Passie, Seifert, and Schneider 2002). Psilocybin has been a focus of clinical research examining its use in combination with existentially oriented and other psychotherapies (Ross et al. 2016). Research has found that it can reduce anxiety and depression in cancer patients (Ross et al. 2016). Psilocybin has been found to reduce amygdala reactivity during emotion processing (Kraehenmann et al. 2014), and in animal studies, to facilitate the extinction of a fear response and increase hippocampal neurogenesis (Catlow et al. 2013).

Despite burgeoning interest, there has not been a comprehensive review of the scientific literature examining these psychoactive drugs in the treatment of PTSD, nor are there guidelines available to support informed practice. Clinical applications of a range of classic hallucinogens have been reviewed for disorders other than PTSD (Bogenschutz and Johnson 2016; Garcia-Romeu, Kersgaard, and Addy 2016). Moreover, two systematic reviews with meta-analyses have examined the use of MDMA-assisted psychotherapy (MDMA-AP) (Amoroso and Workman 2016; Bahji et al. 2019). These found that MDMA-AP demonstrated a high rate of clinical response and large effect size for reducing the symptoms of PTSD. However, these reviews did not appraise the quality of the trials to form judgments about the quality of the evidence base. This review was commissioned by the Department of Veterans' Affairs who were interested in gaining an understanding of the efficacy of the particular hallucinogenic drugs which have been included. The aim was to assess current evidence investigating the efficacy of MDMA, ketamine, LSD and psilocybin, either in combination with psychotherapy or as stand-alone treatments for PTSD.

Methods

The findings of this review are reported according to the Preferred Reporting Items for Systematic Reviews (PRISMA) statement. The research question was formulated using the Population, Intervention, Comparison, and Outcome (PICO) framework in order to structure, contain, and set the scope for the question (Moher et al. 2010). Both RCTs and observational studies were eligible for inclusion. The population of interest was defined as adults with PTSD as determined by diagnosis or cutoff score on a validated measure. The intervention was defined as the administration of MDMA, ketamine, LSD, or psilocybin as either

a stand-alone treatment, or in combination with another treatment, for PTSD. The comparison was defined as any type of control group, including active treatment as well as inactive or "no treatment", placebo, or wait-list alternatives. The outcome was defined as changes in PTSD symptoms and/or diagnostic status.

Eligibility criteria

Studies were included if they (a) investigated MDMA, ketamine, LSD, and/or psilocybin as a treatment for an individual with PTSD, (b) were published in English, and involved adults (18 years of age or older), (c) included a majority of participants (at least 50%) who had been diagnosed with PTSD or had a cutoff score indicating PTSD, and (d) reported outcome data from a psychological measure that assessed PTSD. Studies were excluded if (a) they were not in English, (b) full-text was not available, (c) they were validation studies concerned with the psychometric properties of a given measure, (d) they were animal studies, (e) they were "gray literature" (i.e. research that is unpublished/published in noncommercial form), (f) no quantitative data were reported (e.g. protocol-only studies), (g) they were secondary analyses, (h) they involved couples or group therapy, or (h) they involved children or adolescents (less than 18 years of age). The route of drug administration or dosage and the psychometric properties of the outcome measures used in the each study were not regarded when determining eligibility.

Information sources

We searched the EMBASE (Excerta Medica database), MEDLINE (PubMed), PsycINFO, and The Cochrane Library databases for peer-reviewed literature published from inception to 18th October 2019. The databases were single searched for the following combinations of key words: "*MDMA*" OR "*methylenedioxymethamphetamine*" OR "*3,4-methylenedioxymethamphetamine*" OR "*ecstasy*" OR "*molly*" OR "*LSD*" OR "*lysergic acid diethylamide*" OR "*psychedelic**" OR "*psilocybin*" OR "*magic mushroom**" OR "*mushroom*" OR "*ketamine*" AND "*posttraumatic stress disorder*" OR "*PTSD*" OR "*post*-traumatic stress*" OR "*post*traumatic stress syndrome*" OR "*PTSS*" AND "*intervention*" OR "*pharmacologic**" OR "*treatment*" OR "*pharmacotherapeutic*" OR "*therapy*" OR "*medication*" OR "*psychopharmacology*".

Search and trial selection

Covidence was used for screening and full-text review (Figure 1). Initial screening of titles and abstracts to determine eligibility for full-text review was performed by two reviewers and a blinded independent reviewer checked 10% of the titles and abstracts. Full-text papers were screened for inclusion by two independent reviewers with 90% agreement between reviewers. Discrepancies were resolved through discussion and the involvement of a third reviewer to tie-break.

Data extraction

Data were extracted from all included studies following the full-text assessment. One reviewer extracted the data and one other checked the data, with any disagreement resolved by discussion. In order to assist the narrative synthesis of the included trials, a predefined data extraction template was designed, which included trial description, intervention description, participant characteristics, measures of PTSD, and main findings in relation to PTSD symptoms or diagnosis from pre-treatment to post-treatment.

Assessment of risk of bias and quality assessment

A modified quality and risk of bias checklist (NHMRC 1999) was used to assess the quality of studies on: (1) method of treatment assignment, (2) control of selection bias (3) blinding of outcome assessor (where relevant), and (4) use of standardized outcome assessment. When there was disagreement between the reviewers, a third acted as tie-breaker. The Grading of Recommendations Assessment, Development and Evaluation (GRADE; GRADE Working Group 2004) system was used to rank the overall quality of the evidence. Based on its evidence quality, a study is given one of four grades: high – further research is very unlikely to alter confidence in the estimate of effect, moderate – further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate, low – further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate, and very low – there are high levels of uncertainty about the estimate.

Results

Trial characteristics

From a yield of 2,959 records (see Figure 1), 986 duplicates were excluded and 1,973 articles were screened on title and abstract. Of these, 34 articles were screened at the full-text stage. Ten studies met the inclusion criteria (see Supplementary Table 1); however, one was excluded because it was terminated prematurely after treating six of the anticipated 29 participants (Bouso et al. 2008).

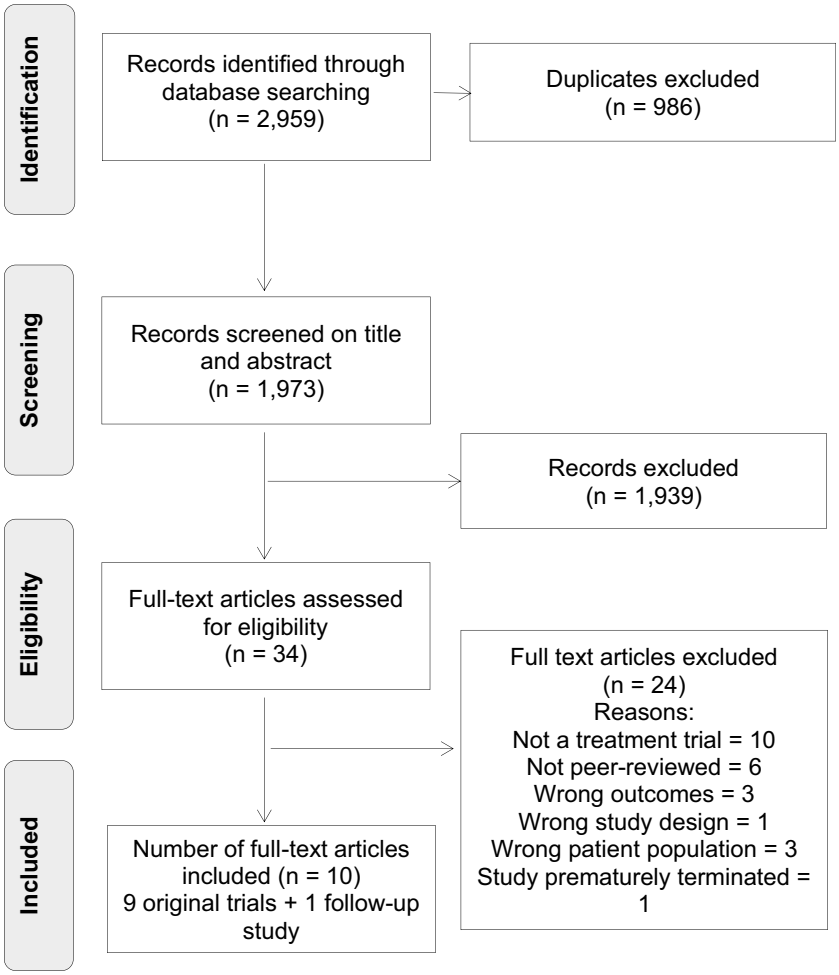

Figure 1. PRISMA flowchart of search for trials. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org).

Three studies involved ketamine as a stand-alone treatment for comorbid PTSD with either major depressive disorder (MDD) or depressive symptomatology, and two studies involved ketamine in combination with psychotherapy for PTSD alone. All of the ketamine studies originated from the United States of America (USA). Four studies concerned MDMA-AP for PTSD, and they originated from Switzerland and the USA. No studies using LSD or psilocybin were found.

Of the studies, five were published in the last 5 years (i.e. 2015–2019). Sample size ranged from 1–41 and the mean age of participants was 26–52.1 years. Females made up the majority of the sample for six of the studies, while the other five had a majority of male participants (inclusive of the male case study). Studies were grouped according to the drug used, and whether the treatment was stand-alone or in combination with psychotherapy. Three of the ketamine studies used ketamine as a stand-alone treatment, while another two used ketamine in combination with psychotherapy. All four of the MDMA studies used MDMA in combination with psychotherapy. Across all drug types, there were five studies that involved a placebo (two active, three inactive), two MDMA-AP studies that compared different drug dosages, and two with no comparison group.

Quality assessment

Seven studies were RCTs, one was a pre-post design, and one was a case study. The RCTs generally had some methodological issues, with key limitations including small sample sizes, and cross-over designs which can lead to the possibility of a "carry-over" of treatment effects. In three of the cross-over design trials, the order of treatments was not randomized. In addition, the ketamine trials generally had very short follow-up periods. Studies were grouped and ranked using GRADE according to the drug type, whether the treatment was stand-alone or in combination with psychotherapy, and in relation to the post-treatment PTSD outcomes (see Table 1).

Table 1. Quality and bias outcomes.

Drug	Study	Design	Treatment Assignment	Control of Selection Bias	Blinding	Outcome Assessment
Ketamine						
Stand-alone	Albott et al. (2018)	Pre-post	N	N	N	Y
Stand-alone	Feder et al. (2014)	RCT	Y	Y	Y	Y
Stand-alone	Womble (2013)	Case study	N	N	N	N
In combination with psychotherapy	Pradhan et al. (2017)	RCT	Y	Y	Y	Y
In combination with psychotherapy	Pradhan et al. (2018)	RCT	Y	Y	Y	Y
MDMA						
In combination with psychotherapy	Mithoefer et al. (2011, 2013)	RCT	Y	Y	Y	Y
In combination with psychotherapy	Mithoefer et al. (2018)	RCT	Y	Y	Y	Y
In combination with psychotherapy	Oehen et al. (2013)	RCT	Y	Y	Y	Y
In combination with psychotherapy	Ot'alora G et al. (2018)	RCT	Y	Y	Y	Y

N = poor quality/high risk of bias; Y = high quality/low risk of bias; RCT = Randomized controlled trial

Summary of the findings

As there were no LSD or psilocybin trials identified, the findings will be specific to ketamine and MDMA.

Ketamine as a stand-alone treatment for comorbid PTSD and depression

The studies of stand-alone ketamine treatment for comorbid PTSD and depression used three different designs: a cross-over RCT, a pre-post design, and a case study design (Albott et al. 2018; Feder et al. 2014; Womble 2013). The double-blind cross-over RCT involved a single-dose intravenous administration of ketamine (0.5 mg/kg), compared to single-dose administration of an active placebo (midazolam, 0.045 mg/kg) (Feder et al. 2014). Participants with PTSD and a minimum Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV) score of 50 were randomized to receive either ketamine or midazolam on the first day of a 2-week follow-up, and then, if they maintained a CAPS score of ≥ 50, were crossed over to infusion with the other agent and followed-up for an additional 2 weeks. Self-reported reductions in PTSD symptoms were significantly greater for the ketamine group relative to the control group, post-treatment (24-h post-administration). One week after infusion, however, mean CAPS scores did not differ significantly between groups. No difference between groups was found for depression symptoms at both post-treatment and one week post-administration. Adverse events included short-lived dissociative symptoms post-administration, elevated blood pressure during administration for which beta-blockers were administered, blurred vision, dry mouth, restlessness, fatigue, nausea/vomiting, poor coordination, and headache.

The pre-post trial involved 15 veterans with comorbid chronic PTSD and treatment-resistant depression who were administered six doses of 0.5 mg/kg ketamine hydrochloride three times per week, across a 12 day period (Albott et al. 2018). Significant improvements were found for PTSD post-treatment, with a remission rate of 80%. Significant improvements were also found for treatment-resistant depression, with a remission rate of 60% post-treatment. Repeated ketamine infusions were associated with transient increases in dissociative symptoms. No other adverse events were reported. The case study, a 26-year-old male veteran with comorbid PTSD and MDD, involved a single-dose administration of 0.5 mg/kg ketamine delivered intravenously with propofol (30 mg). The participant reported subjective improvements in anxiety, depression, restorative sleep and nightmare events following a single-dose intravenous administration of ketamine (Womble 2013). In this case, improvements were not sustained at testing 14 days following infusion. The only adverse event reported was that the veteran had trouble focusing his vision post-infusion.

The quality of evidence for ketamine as stand-alone treatment for comorbid PTSD and depression was graded as "very low" (one pre-post trial, one case study, and one small proof of concept RCT with serious limitations to the quality). Thus, an estimate of the effect of ketamine on PTSD at post-treatment is very uncertain and we have limited confidence that there is a difference in effect for ketamine as a stand-alone treatment for comorbid PTSD and depression, compared to active placebo.

Ketamine in combination with psychotherapy for PTSD

Two double-blind RCTs examined ketamine in combination with psychotherapy for PTSD (Pradhan et al. 2018, 2017). In small pilot RCT by Pradhan et al. (2017), participants with chronic and treatment-refractory PTSD (N =10) were randomly assigned to receive Mindfulness-Based Cognitive Therapy, Trauma Interventions using Mindfulness-Based Extinction and Reconsolidation (TIMBER), plus either a single sub-anesthetic dose of ketamine (0.5 mg/kg; TIMBER-K) or a placebo saline infusion (TIMBER-P). At 24 hours post-infusion, there was a significant decrease in CAPS scores for both groups; however, there was no significant difference between the TIMBER-K and TIMBER-P groups. Participants in the TIMBER-P arm were switched to TIMBER-K once they had a sustained relapse defined as CAPS scores > 50 and PCL scores >51, which persisted for at least 7 days. After cross-over from TIMBER-P to TIMBER-K, it was found that TIMBER-K increased the duration of response on the CAPS by a mean of 24 days. Participants were followed up 12 months later, but CAPS and PTSD results were not reported for this time-point. The authors reported that no clinically significant side effects were observed; however, two participants experienced mild nausea within one-hour post-infusion, which resolved without needing medical intervention.

In a related trial, Pradhan et al. (2018) examined the duration of sustained response for a different sample of individuals who received ketamine in combination with psychotherapy. Participants with treatment-refractory PTSD (N = 20) were randomly assigned to receive TIMBER, plus a single sub-anesthetic dose of ketamine (0.5 mg/kg; TIMBER-K) or plus a placebo saline infusion (TIMBER-P). Participants were followed for 18 months after the initial infusion. At 24 hours post-administration all participants experienced a decrease in PTSD symptoms on the PCL and CAPS. There was no significant difference between groups. The duration of the sustained response was significantly greater for those in the TIMBER-K condition (34.44 ± 19.1 days) compared to those in the TIMBER-P condition (16.50 ± 11.4 days). The presence or absence of adverse events was not reported.

The quality of evidence for ketamine in combination with psychotherapy as a treatment for PTSD was graded as "low" (two small RCTs by the same research group, with some limitations to the quality, e.g. order of treatment not being randomized). Thus further research on the effect of ketamine on PTSD at post-treatment is likely to have an important impact on confidence that there is a difference in effect for ketamine in combination with psychotherapy as a treatment for PTSD compared to a placebo control.

MDMA in combination with psychotherapy for PTSD

Four trials examining MDMA-AP for chronic PTSD which were double-blind cross-over RCTs (Mithoefer et al. 2018, 2011; Oehen et al. 2013; Ot'alora G et al. 2018). The Mithoefer et al. (2011) trial involved participants (N = 20) being randomly assigned to receive either psychotherapy and concomitant active drug (MDMA-AP) (n = 12) or psychotherapy and inactive placebo (n = 8). Participants took part in two 90-min preparatory sessions, followed by two 8–10 h experimental sessions. In the experimental sessions, participants received either MDMA or an inactive placebo, which was administered at the beginning of the session. A supplemental dose of MDMA or placebo was also administered 2.5 hours into the session. Participants spent the remainder of the time resting or in non-directive therapeutic discussion. There were nine integration psychotherapy sessions associated with the three experimental sessions. Improvements in clinician-rated PTSD symptoms and self-reported physical responses to stress were significantly greater in the MDMA group compared to the placebo group. Ten MDMA recipients and two placebo recipients no longer met DSM-IV criteria for PTSD diagnosis using the CAPS-IV following the intervention. Short-term side effects of the drug included elevated blood pressure, pulse, and body temperature, jaw tightness, nausea, feeling cold, dizziness, loss of appetite, impaired balance, and irritability. Long-term data for the MDMA group collected 17 to 74 months after the original study's final MDMA session showed that on average improvements were maintained following the intervention (Mithoefer et al. 2013). Two participants, however, did experience relapse during that period.

Extending on this work, the Mithoefer et al. (2018) trial involved military veterans, firefighters and police officers with chronic PTSD, who were randomly assigned to receive psychotherapy plus: 30 mg (termed "active control"); 75 mg; or 125 mg of MDMA. Consistent with the previous trial, MDMA was administered orally in two 8-h sessions at monthly intervals, with concomitant manualized psychotherapy. The first MDMA session was preceded by three 90-min psychotherapy sessions to establish a therapeutic alliance. One month after the second MDMA-AP session, the 75 mg and 125 mg groups had significantly greater decreases in PTSD symptom severity than the 30 mg group. The effect sizes for these decreases were large. Of the 24 participants who completed the 12 month follow-up, 16 (67%) did not have a PTSD diagnosis. Four serious adverse events occurred, with one deemed as being possibly related to the drug treatment. The participant exhibited a premature ventricular contraction at baseline, and then developed an acute increase in ventricular contractions during the third

open-label session. The participant spent the night in hospital for observation and recovered fully without evidence of cardiac disease.

A trial by Ot'alora et al. (2018) examined MDMA dose response in a sample of people with chronic PTSD. Participants were randomized to receive either 100 mg or 125 mg (active dose) or 40 mg (low dose) during two double-blind eight-hour experimental sessions held one month apart. The intent-to-treat active dose groups had the largest reduction in CAPS total scores at the primary endpoint with mean changes of −26.3 for 125 mg, −24.4 for 100 mg and −11.5 for 40 mg. Statistical significance was only reached for per protocol (p = .03). Cohen's d effect sizes were 0.42 for 125 mg, 0.37 for 100 mg. Reactions on the day of sessions included anxiety, jaw clenching, headache, muscle tension, dizziness, fatigue & low mood. Reactions in the days following the session included sleep-related reactions, low mood, increased irritability and ruminations, however there were no drug-related serious adverse events.

A smaller RCT, reported by Oehen et al. (2013), adopted a similar design to Mithoefer et al. (2011) but compared a low-dose of MDMA (termed an "active placebo", intended to induce only minor alterations in perception and relaxation) with a higher dose. Participants (N = 12) took part in three experimental sessions and 12 non-drug psychotherapy sessions, which followed a format consistent with Mithoefer et al. (2011). There was a significant reduction in self-reported PTSD symptoms at post-treatment; however, at 3-week post-treatment scores did not differ significantly between the treatment groups and all participants still met PTSD diagnostic criteria. At 12-month follow-up (n = 11), five participants no longer met the diagnostic criteria. Side effects included moderate insomnia, loss of appetite, restlessness, tight jaw, thirst, feeling cold, dizziness, headaches, and impaired gait/balance, but there were no serious drug-related adverse events.

The quality of evidence for MDMA in combination with psychotherapy to treat PTSD was graded as "moderate" (four small RCTs suggesting a positive effect, with some limitations to the quality). Further research is likely to have an impact on confidence that there is a difference in effect for MDMA in combination with psychotherapy to treat PTSD compared to either active or inactive placebo controls in combination with psychotherapy.

Discussion

The aim of this systematic review was to assess the efficacy of MDMA, ketamine, LSD, and psilocybin for the treatment of PTSD in adults. No studies were found reporting on LSD or psilocybin. The evidence was divided into two categories, stand-alone treatments (ketamine) and in combination with psychotherapy (ketamine and MDMA). We concluded that the quality of evidence supporting the use of ketamine as a stand-alone treatment for comorbid PTSD and depression was "very low", and in combination with psychotherapy for PTSD was "low". The evidence for MDMA in combination with psychotherapy was graded as "moderate".

For the stand-alone treatments, the evidence for the effectiveness of ketamine for the treatment of comorbid PTSD and depression was rated as "very low". The small amount of published evidence cited above for ketamine in the treatment of PTSD did not indicate a lasting treatment response where ketamine was used as a stand-alone treatment (Feder et al. 2014; Womble 2013). However when ketamine was used in combination with psychotherapy, the effect was sustained for approximately 1 month (Pradhan et al. 2018); therefore, the evidence was given a higher rating than stand-alone ketamine, i.e., "low". In the depression literature, where there is a more developed evidence base, a Cochrane review of RCTs by Caddy et al. (2015) found that the lasting effects of ketamine as a stand-alone treatment are unclear, with limited support for symptom improvement at one to 2-week post-infusion. This suggests that overall, the findings in regards to ketamine for the treatment of PTSD are consistent with the findings of ketamine for the treatment for depression. The effect observed for ketamine in combination with psychotherapy may have been due to the psychotherapy, rather than the ketamine. However, given that there was no control condition in those trials, it is not possible to say this with certainty.

The evidence for MDMA when used in combination with psychotherapy was rated as "moderate". This evidence suggests that MDMA warrants further research and examination for the treatment of PTSD, and several recent papers have been published on the potential therapeutic mechanisms of MDMA in combination with psychotherapy (e.g. Feduccia and Mithoefer 2018; Mithoefer, Grob, and Brewerton 2016). It has been speculated that there are various ways in which MDMA can make it possible to process trauma memories. These include MDMA having an effect on fear extinction and memory consolidation (Feduccia and Mithoefer 2018), allowing for less constrained and less rigid thinking styles (Carhart-Harris et al. 2015), and the prosocial effects possibly promoting a stronger therapeutic alliance and decreasing interpersonal alienation (Dumont et al. 2009).

In this review we identified that MDMA-AP was tested in three very similarly designed trials. These trials produced consistent findings that PTSD symptoms

improved when rated using self-reported measures, and symptom improvements were also found on the CAPS in the trials by Mithoefer et al. (2018) and Ot'alora (2018). The side effects reported in the MDMA trials included moderate insomnia, loss of appetite, restlessness, tight jaw, thirst, feeling cold, dizziness, headaches, and impaired gait/balance (Mithoefer et al. 2018, 2011; Oehen et al. 2013; Ot'alora G et al. 2018). There was one serious adverse event that was deemed to have been possibly related to a drug treatment, with the participant developing an acute increase in ventricular contractions during an open-label session (Mithoefer et al. 2018). Overall safety data has indicated a favorable risk-to-benefit ratio for moderate doses of pure MDMA for treating those with PTSD (Mithoefer et al. 2011, 2013; Oehen et al. 2013). In 2017 the US Food and Drug Administration (FDA) granted MDMA a breakthrough therapy designation for the treatment of PTSD, and a multisite Phase 3 clinical trial is currently underway.

One direction for future research is to test the administration of MDMA in combination with more focused and guideline-recommended PTSD treatments such as Prolonged Exposure or Cognitive Processing Therapy. The findings of this review indicate that MDMA shows promise when combined with non-directive, supportive psychotherapy. However, combining MDMA with more focused treatments is relatively untested. A recent case study of couple's therapy examined combined cognitive behavioral conjoint therapy (CBCT) with MDMA (Wagner et al. 2019). CBCT is a 15-module, three-phase, protocol-based, dyadic treatment for PTSD (Monson and Fredman 2012). The addition of MDMA could potentially accelerate the therapeutic process by improving the therapeutic alliance (Oehen et al. 2013), thereby reducing the time it takes, and the cost of administering lengthy treatment protocols. It has also been posited that the flexibility in cognition that may be offered by MDMA, may address elements of trauma reappraisal targeted in cognitive therapies (Wagner et al. 2019). While testing MDMA in combination with focused PTSD treatments appears to be an obvious next step, it may also be that the prosocial effects of MDMA are most effective when allowed to be expressed more spontaneously and idiosyncratically. In this context, a more structured, guided manualized trauma focused intervention in combination with MDMA may run counter to the active process facilitated by the agent. It has been suggested that it may be important to consider the timing of the psychotherapy relative to the administration of the agent, with patients possibly benefiting from non-directive methods of therapy during the acute drug effects, but there being flexibility for directive and non-directive approaches in the sessions before prior to or following the agent administration (Krediet et al. 2020).

The findings from this review should be considered alongside its limitations. Clinical trial registries were not searched, publications that were not in English were omitted, and reference lists of the included papers were not hand-searched to retrieve any additional relevant trials. Furthermore, a meta-analytic methodology was not applied to synthesize these results quantitatively, due to the small number of heterogeneous trials identified.

PTSD is marked by a high level of treatment resistance, with the use of traditional trauma-focused psychotherapy efficacious for many people, but ineffective for a significant number (Steenkamp et al. 2015). As such, there is a need for a wider array of effective alternative treatment options. Ketamine and MDMA therapies may offer the potential for PTSD symptom reduction or recovery via their actions on the biological mechanisms implicated in PTSD symptoms; however, well-designed research is needed to gain a better understanding of the impact of these therapies on symptoms of PTSD.

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