Exploring the Therapeutic Potential: A Systematic Review of 3,4-Methylenedioxymethamphetamine (MDMA) in the Management of Post-Traumatic Stress Disorder

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Abstract

This systematic review examines the current state of research on the use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy for the treatment of Post-Traumatic Stress Disorder (PTSD). The study explores the historical context of MDMA, its pharmacological mechanisms, and the rationale for its potential therapeutic effects in addressing PTSD symptoms. A thorough examination of clinical trials, randomized controlled trials, and observational studies reveals promising results in terms of safety and efficacy. The review highlights the neurobiological and psychological mechanisms through which MDMA may facilitate the therapeutic process, including enhanced emotional regulation, increased empathy, and improved introspection. Key findings from recent clinical trials, such as the Multidisciplinary Association for Psychedelic Studies (MAPS)-sponsored Phase 3 trials, are presented and discussed. Safety considerations, including potential adverse effects and risk mitigation strategies, are addressed to provide a balanced perspective. The review also discusses the legal and ethical implications surrounding the use of MDMA in therapeutic settings. Additionally, the potential impact of this emerging treatment modality on existing PTSD treatment paradigms and healthcare practices is explored. Overall, this review supports the growing body of evidence suggesting that MDMA-assisted therapy holds promise as a novel and effective approach for individuals suffering from PTSD. While further research is needed to establish long-term safety and efficacy, the findings underscore the potential of MDMA-assisted therapy to contribute to the evolving landscape of mental health treatments for PTSD.

Keywords: MDMA, 3,4-methylenedioxymethamphetamine, PTSD, post-traumatic stress disorder, MDMA-assisted psychotherapy, psychopharmacology

Exploring the Therapeutic Potential: A Systematic Review of 3,4-Methylenedioxymethamphetamine (MDMA) in the Management of Post-Traumatic Stress Disorder

In recent years, the exploration of novel therapeutic approaches for Post-Traumatic Stress Disorder (PTSD) has gained considerable attention within the scientific and medical communities. In the United States, over 6% of the population will have PTSD at some time in their lives; in 2020, there were over 13 million people with this diagnosis (U.S. Department of Veterans Affairs, n.d.). Recognizing the urgent need for effective interventions for individuals suffering from the debilitating consequences of trauma, this study investigates the pharmacological and psychological mechanisms underlying MDMA's impact on trauma processing and its potential to assist in therapeutic breakthroughs. This research is critical, especially if you suffer daily from any of the symptoms of PTSD, which include intrusive thoughts, hyperarousal, negative mood and thoughts, physical health effects, substance use, emotional dysregulation, relationship problems, problems with work or school, and suicidal thoughts or behaviors (Djelantik et al., 2019). Through a meticulous examination of existing literature, clinical trials, and empirical evidence, this paper aims to contribute to the evolving discourse surrounding MDMA's promise as a therapeutic tool for PTSD, shedding light on its potential to redefine conventional approaches to trauma-focused psychotherapy.

Background and Significance

MDMA is a much older drug than most are aware of. It was first developed in 1912 by Merck as a compound. Initially reported as an appetite suppressant, it was developed to synthesize medications to control bleeding (Davey, 2021). It did not undergo testing on humans or animals and was nearly forgotten. Later, it became popular with some therapists in the 1970s and 80s when it was used as an adjunct to therapy sessions (Passie, 2018). They claimed it

enhanced communication, promoted relaxation, increased motivation to participate in therapy, reduced depression and anxiety, and increased the therapeutic bond between patients and their therapists (Passie, 2018). MDMA reduces or eliminates fear and anxiety, allowing patients to access their traumatic emotions and ease the inability to express their thoughts and fears (Hendy, 2020). This made it a favorite among some psychotherapists at the time. However, in 1985, an emergency ban was placed on MDMA by the Drug Enforcement Agency (DEA) due to its widespread availability "on the streets," making it a Schedule 1 drug and putting an end to any research (National Institute on Drug Abuse, 2017). A Schedule 1 drug is said to have no currently accepted medical use and a high potential for abuse and "cannot be prescribed, dispensed, or administered" (NIH National Library of Medicine, 2023). Although it was made a Schedule drug by the DEA, a non-profit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS) lobbied the Food and Drug Administration (FDA) to allow it to be studied on the basis that the therapeutic effects of MDMA had not been studied and were not absent (U.S. Food & Drug Administration [FDA], 2023). They had discovered through research the potential that it had. After 15 years of hard work, their efforts paid off, and in 2001, they were granted the first MDMA study protocol (Hendy, 2020). If the FDA determines viable therapeutic potential, they can recommend a drug to be rescheduled to the DEA (FDA, 2023). This is something that they are still working on through their research, but it has not yet occurred.

From a public health standpoint, PTSD is a severe problem. A lifetime prevalence of approximately 6.8% means this disorder affects an estimated 7.7 million Americans annually (Gorman et al., 2020). PTSD has also been shown to have a high level of comorbidity. It often coexists with substance use disorders, mood disorders, anxiety disorders, and depression (Gorman et al., 2020). Having been studied as a treatment for alcohol use disorder (AUD), it

was not found to have a significant impact; however, since AUD is often closely associated with PTSD, it shows promise as a potentially successful treatment when approached from this direction (Nicholas et al., 2022). Although some can overcome PTSD, many have lifelong and devastating symptoms. The comorbidities further complicate treatment and increase the overall burden on the healthcare system.

MAPS recognized the need for a more effective treatment and knew it needed to come sooner rather than later (Morgan, 2020). The first published study that MAPS backed was designed to investigate the effects of a single dose of MDMA on women who had chronic PTSD due to sexual assault. The study group was small, with 29 women receiving varied amounts from 50 to 150mg (Bouso et al., 2008). The women were divided into five groups. Group 1 (50mg) and Group 5 (150mg) had four participants, with three receiving the MDMA doses and one receiving a placebo. In comparison, Groups 2 (75mg), Group 3 (100mg), and Group 4 (125mg) had seven participants, with five receiving the dose and two receiving the placebo (Bouso et al., 2008). The design was to have 21 subjects receiving the MDMA doses and eight receiving the placebo; however, the study was suddenly shut down over political pressure after only six subjects had received treatment. Although the study was incomplete, the data received from the six participants was presented as a baseline study in the hopes that it would display the need for further research. The six women ranged in age from 29 to 49, had varying education levels, and were diagnosed with PTSD due to varying forms of sexual aggression (Bouso et al., 2008). They all had participated in the three non-drug psychotherapy sessions before the experimental session and the three after. The experimental session was approximately eight hours in duration. It consisted of administration of the MDMA, time for relaxation and medication to take effect, and discussion between the participant and the therapist about their trauma and time to work through their feelings and dive further into the traumatic event. The

therapist and the participant then shared a meal, and when the subject had returned to her "ordinary state of consciousness," she was driven home by a friend or significant other (Bouso et al., 2008). This study was the first fully approved, controlled study in the world to display the possibility that MDMA could be helpful as an adjunct to psychotherapy to reduce the symptoms of PTSD with little or no adverse effects (Bouso et al., 2008). It created a question that only further studies with larger sample sizes could answer.

According to the *Diagnostic and Statistical Manual of Mental Disorders 5th Ed.* people with PTSD are associated with high levels of disability in work, school, or relationships due to re-experiencing the trauma, impaired functioning, poor reactivity to situations, sleep disturbances, and occupational and familial stress (American Psychiatric Association [APA], 2013). The prevalence of PTSD has continued to increase with people suffering from nonresponse and high treatment dropout rates (Ot'alora G et al., 2018). Due to the high incidence and overall prevalence of PTSD, it is imperative that treatment modalities that have displayed early success be further investigated, and more studies be performed. Sleep disturbances are one of the most reported symptoms. In one of the most extensive studies measuring the effects of MDMA on the sleep disturbances associated with PTSD, it was determined that the MDMA group had marked improvement in sleep disturbances and a noticeable reduction in PTSD symptoms (Ponte et al., 2021). Sleep disturbances have been found to exacerbate the severity of PTSD symptoms greatly (Dietch et al., 2019).

Post-traumatic stress has been shown to have some improvement with psychotherapy and psychopharmacology, but it does not have great success. Currently, only selective serotonin reuptake inhibitors (SSRIs), paroxetine, and sertraline are FDA-approved for the treatment of PTSD (Stahl, 2020). Unfortunately, an estimated 40-60% of patients do not respond to these medications (Mitchell et al., 2021). Psychotherapy has a lower success rate because of treatment

failure, dropouts, and difficulty with follow-up interviews (Feduccia et al., 2019). One of the forms of psychotherapy, fear extinction training, has shown some improvement, but when augmented with MDMA dosing, the participants did not achieve complete fear extinction; however, they retained a reduction in fear-potentiated symptoms (Maples-Keller et al., 2022). More reliable treatment is needed, and this study shows the need for further research.

Review of the Literature

Several clinical trials have been performed, but the trials are few and far between due to the legality and study difficulties. MDMA is classified as a Schedule 1 controlled substance, which means it is considered to have a high potential for abuse, has no accepted medical use, and is illegal to possess (Jones & Nock, 2022). In 2017, the FDA granted MDMA "breakthrough therapy" status, which would allow for expedited studies using MDMA (Feduccia et al., 2019). Three phased trials were reviewed, pooled, and their data analyzed (MP-2, MP-6, MP-8). They were of similar study designs; two of the studies, MP-2, conducted by Ot'alora et al (2018) and MP-6, conducted by Mithoefer et al (2018), are from the randomized phase 2 clinical trials, and MP-8, conducted by Mitchell et al (2021) is a randomized, double-blind, placebo-controlled phase 3 study. These are all published studies. Study sites were Boulder, CO (MP-2) and Charleston, SC (MP-6), and they were compiled from study sites in the US, Canada, and Israel (MP-8). They had different study sizes: 28 (MP-2), 26 (MP-6), and 90 (MP-8). All the study groups required a preexisting diagnosis of PTSD, and the MP-2 and MP-6 required that the participants had a CAPS-IV score over 50. MP-8 measured the difference in the CAPS-IV score at baseline and two months after the last experimental session. The CAPS scores, based on the DSM-IV or V, are measurements of the diagnostic status and symptom severity of PTSD symptoms and would provide continuity in the clinical utility of a measurement system (Weathers et al., 2018). When the cases were initiated, written consent was established. In MP-

2, the participants were given an active dose (100 or 125mg) or 40mg during two double-blind eight-hour experimental studies, and participants were given a supplemental dose (62.5, 50, or 20mg) 90 minutes after the initial dose, if not contraindicated (Ot'alora G et al., 2018). Each session was spaced a month apart. MP-6 administered 30, 75, or 125mg doses, depending on the dose groups, in two blinded experimental sessions 3–5 weeks apart (the initial dose was followed by a subsequent dose that was half the initial approximately 90 minutes to two hours later) (Mithoefer et al., 2018). In MP-8, the exact amounts given are not provided in the study because the focus was to demonstrate a reduction in CAPS-IV scores, depression scores (using the Beck Depression Inventory-II), and suicidality (using the C-SSRS score) (Mitchell et al., 2021). All the studies were designed to gather data on the efficacy and success of MDMA in treating PTSD.

MP-2 showed, consistent with prior research, that there was a significant reduction in CAPS-IV scores in the active dose groups compared to the 40mg group (a 30% drop compared to a 16.7% drop) (Ot'alora G et al., 2018). The crucial part of this study is that it showed a continued reduction in the 12-month follow-up, with 76% (n=25) of the study participants not meeting the criteria for a PTSD diagnosis (Ot'alora G et al., 2018). They also reported significant reductions in secondary outcome measures (sleep, depression, and dissociation) compared to their initial baseline (Ot'alora G. et al., 2018). MP-6 compared CAPS-IV scores at baseline and 12 months; all showed a statistically significant improvement ($p<0.0001$) (Mithoefer et al., 2018). This study showed that it was well tolerated with few significant side effects or adverse reactions and secondary reductions in depression, sleep quality, and dissociative symptoms with low treatment discontinuation rates (7.7%, which was not correlated with the dose) (Mithoefer et al., 2018). MP-8 showed that regardless of the dose, there was a statistically significant ($p<0.0001$) reduction in CAPS-IV score, Sheehan Disability Score (SDS), and Beck Depression Inventory-II (BDI-II) from baseline and at two months after the last

experimental session (Mitchell et al., 2021). In one additional study, MDMA-assisted psychotherapy showed higher levels of post-traumatic growth and reductions in PTSD symptom severity than the placebo group (Gorman et al., 2020). One of the most impressive parts of this study was that at the 12-month follow-up, the patients still displayed these high growth levels and lower symptoms (Gorman et al., 2020).

Purpose and Clinical Question

In 2018, the total economic burden of PTSD was estimated at over $232 billion (Davis et al., 2022). This number goes beyond direct healthcare costs, including unemployment, homelessness, psychotherapy, and continued research and training costs. This systematic review is intended to show that in adults, the administration of MDMA-assisted psychotherapy, compared to traditional pharmacology or psychotherapy alone, results in a superior reduction of PTSD symptoms. Finding a successful treatment now for PTSD is essential to help alleviate suffering, improve mental health, and enhance the overall well-being of individuals affected by trauma. It is important to note that individuals who undergo MDMA-assisted therapy often report sustained improvements in PTSD symptoms, suggesting that the therapy may have a lasting impact on the way traumatic memories are processed and integrated. So, can MDMA administration with the use of psychotherapy become a viable treatment for PTSD?

Conceptual Framework

A Biopsychosocial Model was used to identify and determine the best ways to integrate the biological, psychological, and social factors involved in understanding and treating PTSD. Through this model, George Engel showed us a “deep appreciation of the illness experience itself and the many sociocultural factors that come to bear on our appreciation of illness” (Lee & Oldham, 2022, p. 188). When reviewing the context of MDMA-assisted therapy, we acknowledge the biological effects of MDMA on the brain, the psychological impact on the

processing of trauma and the relief of symptoms, and the social aspects of psychotherapy and various support networks. There is still so much that we need to learn. Further research would allow us to understand better how MDMA affects the brain and how the brain processes emotions.

Project Design

This systematic review of the literature using MDMA to treat PTSD was developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A Biopsychosocial framework guided the review. It is researched comprehensively by considering the biological, psychological, and social factors contributing to the condition and its potential treatment. Researchers need to understand how MDMA interacts with the brain, the central nervous system (CNS), and its effects on neurotransmitters such as serotonin, norepinephrine, and dopamine. Using neuroimaging studies, researchers can identify the specific brain regions and networks affected by MDMA in people with PTSD. One such study showed how MDMA causes an increased amygdala response and increased vivid recollection of positive memories (Carhart-Harris et al., 2013). Researchers can also explore the pharmacokinetics of MDMA to study its metabolism and any adverse effects to help develop safe doses that minimize risks. By considering that individuals may react differently to MDMA, researchers can study these genetic variations that can influence responsiveness and the body's metabolism. The studies must contain standardized measures of trauma to assess the types and severity of trauma, psychological outcomes, and any improvements or setbacks the participants experience. The analysis of successful controlled trials will assist in developing MDMA-assisted therapy protocols. They will provide the necessary research to set guidelines for therapeutic settings, the therapist's role, any preparation, and integration of the process. These studies will also help

determine social support networks' role in MDMA-assisted therapy. Assessing the impact of the treatment environment and support system will be necessary for protocol development. Assessing cultural considerations on this type of therapy will also be necessary. Developing research plans and navigating the ethical and legal challenges associated with using MDMA, consent, regulation, and patient confidentiality through a biopsychosocial framework will be paramount in continuing to study MDMA's potential as a treatment tool for PTSD.

Search Strategy and Selection Process

A search strategy was developed to retrieve references relating to the treatment of PTSD using MDMA using the following keywords: PTSD, MDMA, 3,4-methylenedioxymethamphetamine, MDMA-assisted psychotherapy, posttraumatic stress disorder, and ecstasy. These keywords were used in the CINAHL, PubMed, and Medline databases. The details of each strategy can be seen in the PRISMA Flow Diagram (Table 1). There were a total of 87 articles found, with 58 excluded or content and duplicity. Nineteen were assessed for eligibility, and ten were excluded. Seven were excluded for using cannabis and MDMA, one for focusing on ethnoracial differences, one for focusing on eating disorders and PTSD, and the final for using talk therapy instead of psychotherapy. This left nine articles for inclusion. The searches were conducted between 2018 and 2023, plus the seminal study by Bouso et al. to maximize yield. All searches included English literature. Only one article was found and excluded because it did not meet the criteria. Articles were excluded if they used other psychedelics along with MDMA, focused on a specific type of therapy, or focused more on a social issue instead of using MDMA as the focus of treatment. Articles were manually searched to ensure that no exclusion criteria were missed by electronic search. The PRISMA flow diagram (Table1) visualizes the search strategy and results of this systematic review. Each of the 23 articles was screened using the Rapid Critical Appraisal Questions for Randomized

Clinical Trials (RCT), with a cutoff of 0.7, found in Appendix C to exclude further and finalize the nine articles used in this systematic review.

Synthesis Method

A detailed Evidence Synthesis Table was used to structure and organize the key findings from different studies (see Figure 1). Each study was listed by the first author's last name and the year of the study. The potable was used to record the following data, and if the theoretical framework was provided, it was listed in the next section. The research design was determined as this was part of the exclusion criteria. Then, the duration, sample size, and setting were listed. Although it was not an exclusion criterion, the participant's age, gender, and ethnicity were noted. The baseline PTSD severity scores using the CAPS-IV scale were noted in each study. The dose of MDMA, frequency, any given adjuncts, and particular methods were listed in the table. The results, including any statistical significance and brief findings of treatment success with MDMA for PTSD, were recorded. Each study was given a Quality Appraisal Rating using the Rapid Critical Appraisal Tool (see Appendix C), and any limitations were noted. All conclusions were noted, and critical decision-making details were recorded.

Methods

This literature search was performed using CINAHL, Medline, and PubMed databases. As seen in the flow diagram (Figure 1), a total of 213 articles were discovered. Forty-seven duplicate records were removed. Automation tools declared 77 publications as ineligible. Two papers were removed for ineligible content. Eighty-seven articles were further screened for content. Out of these, 58 were excluded for varied focus not specific to MDMA and PTSD solely. They were excluded because they did not have a control group, or it was an opinion piece. Most of the exclusions were review articles and not controlled trials or did not have relevant outcomes or interventions. On final screening, seven articles were further excluded

because they included cannabis and MDMA as a treatment. One article focused on ethnoracial reasons for MDMA's success, and one article blamed the MDMA use for an increase in previously diagnosed eating disorders. The last exclusion used talk therapy instead of psychotherapy, separating it from all the other included studies. This left the final nine articles.

The studies in the evidence table (Table 1) are focused on demonstrating the efficacy of using MDMA with psychotherapy to treat PTSD and its associated symptoms. The studies used were double-blind, randomized, placebo-controlled trials in either phase 2 or 3. Their sample sizes ranged from 6 (Bouso et al., 2008) to 90 (Mitchell et al., 2021) (Nicholas et al., 2022). Five articles used the CAPS-IV scales to assess PTSD symptoms, one used the SSSPTSD scale, one used a fear retention measure scale, and the last used the Beck's Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI). The CAPS-IV was updated to the CAPS-5 when the DSM-5 was published in 2013. This assessment measures the onset and duration of symptoms, the overall severity of symptoms, the impact of symptoms on work and overall functioning, any improvement in symptoms since the last CAPS assessment, and the validity of responses (Weathers et al., 2018). The SSSPTSD scale is the Spanish version of a PTSD symptom scale (Bouso et al., 2008). The BDI and the STAI are standardized measurements of anxiety (Carhart-Harris et al., 2013). The primary focus of each study was to demonstrate the positive effects of MDMA on PTSD and its associated symptoms, such as sleep disturbances, substance use disorders, and fear. This concept has very little research due to the legalities surrounding the ability to study it. The hope is that presenting studies, although with mostly small sample sizes, will encourage further research into this treatment modality.

Results

The main theme that is present across all studies is that MDMA has beneficial effects on symptoms of PTSD. One study displayed an increase in positive subjective responses to good

memories and a decrease in negative responses to bad memories (Carhart-Harris et al., 2013). This premise was the driving force in the seminal study performed in 2008 with six victims of sexual assault (Bouso et al., 2008). Although it was designed to show safety when using MDMA, it was also used to display the improvement in memories of a previous traumatic experience (Bouso et al., 2008). Another study, years later, correlated both safety and a decrease in alcohol use disorder (AUD) / substance use disorder (SUD) with the administration of MDMA and psychotherapy during treatment (Ot'alora et al., 2018). A study by Nicholas in 2022 also examined the use of MDMA, its effects on AUD/SUD, and how it was shown to be safe and well tolerated (Nicholas et al., 2022).

There are only two FDA-approved treatments for PTSD currently: paroxetine and sertraline (Stahl, 2022). One study aimed to show that MDMA was a more effective treatment because it significantly reduced PTSD symptoms (CAPS-5 scores) and reduced the Sheehan Disability Score (Mitchell et al., 2021). The studies that investigated the use of MDMA for sleep disturbances (Ponte et al., 2021), its effects on PTSD symptom reduction (Gorman et al., 2020), and its effects on fear extinction and learning (Maples-Keller et al., 2022) show promising initial research on the benefits of MDMA on these symptoms that can be life-threatening to patients who suffer from PTSD. Surprisingly, there were no more articles that focused on PTSD treatment in military personnel since it is such a monumental issue.

Synthesis Across Studies

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Discussion

In the limited number of studies that were found, there was a consistent positive trend and evidence to support the need for further research on using MDMA to treat PTSD. In the statistical analysis of the data compiled in these initial studies, phase 2 and 3 trials, and pooled research studies, statistical evidence supports the use of MDMA for PTSD treatment and warrants further studies.

Recommendations from Findings

Due to the legality and stigma attached to the use of MDMA, there have not been any other research projects completed. This treatment area is still in the early stages and has much potential; however, current practice recommendations cannot be made at this time.

Limitations

The most restricting limitation present in all the studies is the legality of the use of MDMA in research. It is still classified as a Schedule 1 drug and requires special permissions for its use in research. Research is further hindered by the stigma attached to its use. MDMA is largely known as a club or recreational drug, and its medicinal use is frequently overlooked. In the studies listed in the evidence table (Table 1), their primary limitation was study size. None of the studies would be considered racially diverse. Another study focused on the effect of MDMA on best and worst memories, but the participants were healthy and did not meet the requirements for a PTSD diagnosis (Carhart-Harris et al., 2013).

Conclusions and Implications

In conducting this review, it became very apparent that more research is needed on this subject. The use of MDMA appears to have such potential in treating a chronic illness, PTSD is very costly, has high mortality rates, and is very dysfunctional to the patient, their family, their career, and their overall mental health. This treatment modality has shown such efficacy in the treatment of PTSD, and further research is desperately needed. Future studies on the use of MDMA for the treatment of this disorder should be administered in controlled settings where the symptom measurement scales can be uniform, participants can be safely assessed and monitored, and results can be gathered and followed up on. The use of MDMA for treating such a devastating chronic illness has such possibilities and warrants further research to add a new tool to the mental health provider's toolbox.

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Figure 1

Flow Diagram

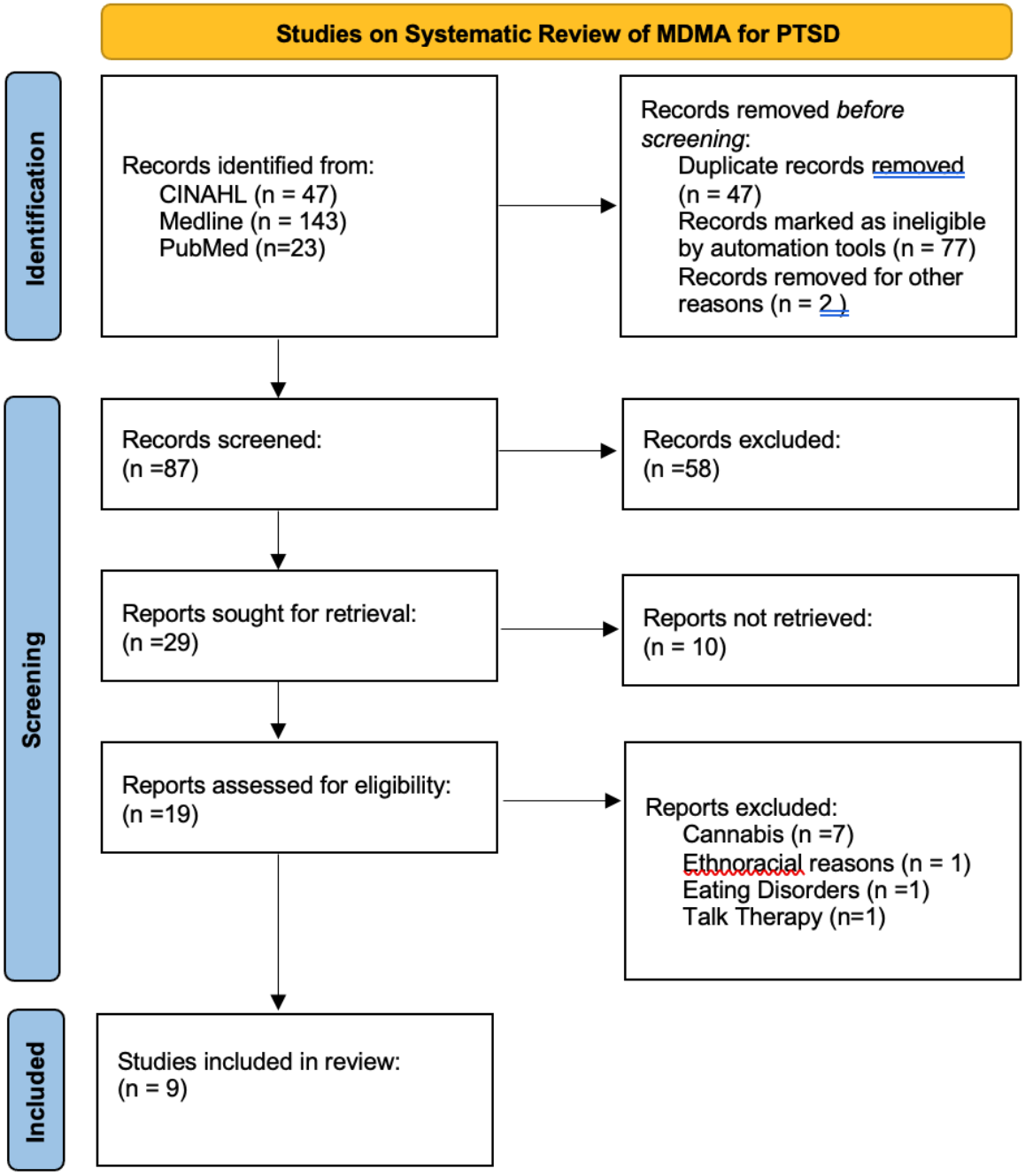

Table 1

Evidence Synthesis Table

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
Bouso, 2008	Investigate safety of PTSD for treatment of PTSD in women	N/A	Dbl-blind, RPCT, ascending dose	N=6; women who were victims of sexual assault; Madrid, Spain	5 increasing doses of MDMA and therapy. Measurement of baseline SSSPTSD and 3, 6, 9, and 12 months.	Reduction in SSSPTSD scores. No increased symptomology, no adverse effects on vital signs.	**Quality Appraisal Rating**: 0.8 **Limitations** Political pressure shut down study before completion/after only 6 treated.	World's first fully approved study on safety of MDMA administration. Higher doses of MDMA showed most improvement in PTSD symptoms.
Carhart-Harris, 2013	Effect of MDMA on best and worst memories.	N/A	Dbl blind, RPCT;	N = 17, London, UK. Healthy, MRI compatibility, present mental health	12 memory cues – (6 good, 6 bad) collected; MRI scan w/ vis/aud cues; BDI & STAI before & after	Significant positive correlation (p=0.032, R^2= 0.19)	**Quality Appraisal Rating :** 0.9 **Limitations:** Study used healthy patients – not PTSD	MDMA ↑subjective response to good memories & ↓bad. Supports primary hypothesis
Gorman, 2020	Measurement of post traumatic symptom reduction after MDMA-assisted psychotherapy	N/A	Pooled research study; triple-blind crossover designs	N=60; DSM5 criteria for PTSD; CAPS-IV ≥50	Results analyzed for different doses and CAPS-IV score	Confirm reduced symptom severity and improved PTSD symptoms after MDMA/therapy treatment. MDMA save in controlled environment.	**Quality Appraisal Rating :** 0.8 **Limitations:** varied sample size, study design, tested doses. Disproportionately white/Caucasian	Future research of MDMA assisted psychotherapy is needed. Measurements of PTG important. Treatment effects are positive for this therapy
Maples-Keller, 2022	Effect of MDMA on fear	N/A	Parallel grp; RPCT	N=34; age 21-55, healthy	Fear acquisition, extinction	MDMA grp retained extinction	**Quality Appraisal Rating :** 0.9	MDMA has positive effect on fear extinction training

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
	extinction learning & prevention			adults; Atlanta, GA – Emory U.	training, med admin. Fear retention measure.	training. (x^2=7.29, p=0.007)	**Limitations:** small sample size not representative of general public	retention; improve therapeutic response to PTSD treatment
Mitchell, 2021	MDMA more effective than SSRIs on PTSD	N/A	Dbl blind, RPCT, phase 2	N=90; severe PTSD w/ comorbidities; multi-site- US, Canada, Israel	Measure CAPS-5 at baseline to 18 weeks. MDMA and therapy	MDMA grp had improved CAPS-5 (p<0.0001, d=0.91) and SDS (p=0.0116, d=0.43)	**Quality Appraisal Rating :** 0.9 **Limitations:** small size; lacks racial diversity	MDMA asst. therapy reduces PTSD symptoms and decreases SDS score more than SSRIs.
Mithoefer, 2018	MDMA as effective treatment for PTSD in service personnel	N/A	Rand, dbl blind, dose-response, phase 2 trial	N=26; 18+ year old, service personnel, chronic PTSD; Charleston, SC	Caps-5 score and 3 doses of MDMA w/psychotherapy. Reassess at 12 mos.	75mg &125mg groups had greater mean change in CAPS-5 score(-58.3(SD9.8) and -44.3 (28.7)) p=0.001; than 30mg grp (11.4912.7))	**Quality Appraisal Rating :** 0.9 **Limitations:** small sample size and lack of racial diversity.	CAPS-5 score significantly reduced from baseline at 12-month follow-up; effective and well tolerated treatment for PTSD.
Nicholas, 2022	Effects of MDMA on alcohol and substance use in PTSD	N/A	RPCT, phase 3 trial	N=90; severe PTSD, mild or mod in early remission AUD or CUD; CAPS-5 ≥35; 15 sites, US, Canada, Israel	Baseline AUDIT/DUDIT & CAPS-5 score; 3 x 8hr MDMA session - 90 min therapy sessions 1 week apart over 3-4 wks	AUDIT change scores and baseline CAPS-5 in MDMA group (r=0.32, p=0.04)	**Quality Appraisal Rating :** 0.9 **Limitations**: did not use severe ASUD; self-reporting.	MDMA w/therapy had decrease in AUD from baseline in pts w/PTSD. Studies show MDMA is safe and well tolerated treatment for PTSD.
Ot'alora, 2018	Effects of MDMA on	N/A	Two-arm, RPCT, dbl-	N=28; CAPS-5≥35, could have mild	CAPS IV measured; 3 x 90min therapy	Reduction in all MDMA groups of CAPS-IV scores;	**Quality Appraisal Rating :** 0.9	Study displayed promising efficacy

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
	AUD/SUD in PTSD treatment		blind; phase 2	AUD/CUD; Boulder, CO	prep sessions, 2 x experimental sessions1 month apart, follow up 2 months after 3rd session & at 12 mos.	at 12 months – 76% of participants in MDMA group did not meet criteria for PTSD diagnosis.	**Limitations:** Study was 68% female and 93% white. Small sample size	and safety results for treatment of PTSD with MDMA Supportive evidence for more research
Ponte, 2021	Improved sleep quality in MDMA assisted therapy for PTSD treatment	N/A	4 x rand., dbl-blind phase 2 studies; 4 sites in US, Israel, and Canada	N=63, CAPS-IV ≥50, could have anxiety or depression, no major medical conditions. must weigh over 48kg.	8hr blinded sessions with MDMA or placebo and therapy 3-5 weeks apart. PQSI measured at baseline and after each session.	More in MDMA group (53.2%; *n*=61; *p*=003) had PSQI drop of 3 or more points compared to control – 12.5%. Less daytime dysfunction reported	**Quality Appraisal Rating :** 0.8 **Limitations:** Small study size; 85.7%white/Caucasian; sleep symptoms subjective	Change in sleep quality positively correlated with change in PTSD symptom severity. MDMA therapy suited to promoting sleep regulation in patients' w/PTSD.

Abbreviations: ASUD = Alcohol and Substance Use Disorder, AUD = Alcohol Use Disorder, AUDIT = Alcohol Use Disorder Identification Test, BDI = Beck Depression Inventory, d = days, CAPS-IV = Clinician Administered PTSD Scale for DSM-IV, CAPS-5= Clinician Administered PTSD Scale for DSM-5, CUD = cannabis use disorder, dbl = double, DUDIT = Drug Use Disorder Identification Test, hr(s) = hour(s), MDMA = 3,4-methylenedioxymethamphetamine, MRI = magnetic resonance imaging, N = sample size, PTG = Post Traumatic Growth, PTGI = Post Traumatic Growth Inventory, PTSD= post-traumatic stress disorder, PQSI = RCT = randomized control trial, RPCT = randomized, placebo-controlled trial, rand = randomized, SDS – Sheehan Disability Score, SLE = specific life events, STAI = State-Trait Anxiety Inventory, SUD = Substance Use Disorder, SSSPTSD = Symptoms Scale for Post-Traumatic Stress Disorder, vis/aud = visual / auditory,

Appendix C

Appendix C: Rapid Critical Appraisal Questions for Randomized Clinical Trials (RCT)

VALIDITY			
1. Are the results of the study valid?	1 pt	0 pts	0 pts
a. Were the participants randomly assigned to the experimental and control groups?	Yes	No	Unknown
b. Was random assignment concealed from the individuals who were first enrolling participants into the study?	Yes	No	Unknown
c. Were the participants and providers blind to the study group?	Yes	No	Unknown
d. Were reasons given to explain why participants did not complete the study?	Yes	No	Unknown
e. Were the follow-up assessments conducted long enough to fully study the effects of the intervention?	Yes	No	Unknown
f. Were the participants analyzed in the group to which they were randomly assigned?	Yes	No	Unknown
g. Was the control group appropriate?	Yes	No	Unknown
h. Were the instruments used to measure the outcomes valid and reliable?	Yes	No	Unknown
j. Were the participants in each of the groups similar on demographic and baseline clinical variables?	Yes	No	Unknown
RELIABILITY			
2. What are the results?			
a. How large is the intervention or treatment effect (NNT, NNH, effect size, level of significance)?	__	__	__
b. How precise is the intervention or treatment (CI)?	__	__	__
APPLICABILITY			
3. Will the results help me in caring for my patients?			
a. Were all clinically important outcomes measured?	Yes	No	Unknown

VALIDITY			
b. What are the risks and benefits of the treatment?			
c. Is the treatment feasible in my clinical setting?	Yes	No	Unknown
d. What are my patient's/family's values and expectations for the outcome that is trying to be prevented and the treatment itself?			

Would you use the study results in your practice to make a difference in patient outcomes?

- If yes, how?
- If yes, why?
- If no, why not?

Additional Comments/Reflections:

Recommendation for article use within a body of evidence: