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Is MDMA a Safe and Effective Adjunct for Treatment of Posttraumatic Stress Disorder

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by

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Abstract

Background: Post-traumatic stress disorder (PTSD) is a common mental health disorder that affects many Americans and leads to considerable morbidity and mortality. While there are a range of therapies to treat PTSD, treatment resistance is high, leading to a chronic condition in many patients. In recent years, attention has been turned to the use of novel drugs, such as 3,4,-methylenedioxymethamphetamine (MDMA) as a treatment for PTSD.

Aim: The purpose of this literature review was to assess the safety and efficacy of MDMA use in the treatment of PTSD.

Results: MDMA is a schedule I drug, therefore research into its use is limited. This literature review reports on the results of six phase 2 trials (n=103) and the only phase 3 randomized control trial (n=92). Results of the phase 2 trials found that 52.7% of the experimental group no longer met criteria for PTSD compared to only 22.6% of those in the control group. Results of the phase 3 trial found that MDMA produced statistically significant reductions in CAPS scores of patients ($p<0.0001$, $d=0.91$) as well a decrease in SDS scores ($p=0.0016$, $d=0.43$).

Conclusion: MDMA seems to be a safe, effective, and long-lasting treatment option for patients with treatment resistant PTSD. However, additional studies involving larger sample sizes and longer follow-up are warranted.

Keywords: *3,4,- methylenedioxymethamphetamine, MDMA, Post-traumatic stress disorder, PTSD*

Introduction

Posttraumatic stress disorder (PTSD) is a complex mental disorder that results from direct exposure to a traumatic event, witnessing a traumatic event, being exposed to the results of a traumatic event, or learning of a traumatic event happening to a loved one (American Psychiatric Association, 2020). In most individuals, once the threat has passed, the fear also subsides, but in a certain subset of patients, the fear component remains and can cause significant disruptions in one's life. Symptoms of PTSD include recurrent memories or flashbacks, avoidance of places, activities, or individuals associated with the event, negative changes in one's attitude, trouble sleeping or concentrating, and an increase in angry outbursts or aggressive behavior. In addition to these symptoms, individuals with PTSD are more likely to have co-morbid conditions such as depression, anxiety, and substance abuse (Sessa, 2016).

According to the American Psychiatric Association (APA, 2020), nearly 3.5% of Americans suffer from PTSD every year, with an estimated 1 out of 11 being affected over the course of their lives. These studies found that women are twice as likely to be affected as men, and those of Latinx, African American, and Native American descent are disproportionately affected. Research conducted by the U.S. Department of Veterans Affairs (U. S. Department of Veterans Affairs, n.d.) found that the most common causes of PTSD were military combat, childhood abuse/trauma, and sexual assault.

Statement of the Problem

While PTSD is the only mental disorder with a known cause, little is known about the neurobiology of PTSD and why certain individuals fail to recover from the traumatic event. Due

to the lack of knowledge on the mechanisms of the condition, treatment options for PTSD are limited with very few patients achieving full remission (Kelmendi et al., 2016). There is debate among the top agencies involved in PTSD, (Veterans Affairs/Department of Defense (VA/DoD), American Psychiatric Association (APA), and the International Society for Traumatic Stress Studies (ISTSS)), as to whether psychotherapy or pharmacotherapy is the preferred first line treatment (Lee et al., 2016). Unfortunately, there is little head-to-head research comparing these two interventions, leaving providers without a clear choice for treatment.

Additionally, research into these interventions has shown that neither treatment option offers promising success rates. The American Psychological Association currently has strong recommendations for 4 types of therapy: cognitive behavioral therapy (CBT), cognitive processing therapy (CPT), cognitive therapy, and prolonged exposure therapy (PET) (American Psychological Association, 2017). Response rates to psychotherapy is moderate, around 50%. In addition, research has found that dropout rates in therapy groups exceed 50%. Reasons for drop out include incompatibilities with therapists, time requirements, and inability to tolerate the trauma-based strategies. (Hoskins et al., 2021). Pharmacotherapy consists of SSRIs, mainly sertraline and venlafaxine. And while compliance levels are higher, the response rate is less than 60%, with less than 30% achieving full remission (Berger et al., 2010).

It has become apparent that a more effective treatment for PTSD is necessary. New research has shown that the common street drug Ecstasy, otherwise known as 3, 4-methylenedioxymethamphetamine (MDMA), may be the key.

Research Question

Is MDMA a Safe and Effective Adjunct for Treatment of Posttraumatic Stress Disorder?

Methods

A literature review was performed using electronic search databases; PubMed, Clinical Key, and Embase. Both keyword and mesh terms were used to define a set of the literature discussing the use of MDMA in PTSD treatment as well as the epidemiology of PTSD and the history of MDMA. The search revealed a total of 116 studies. There were several studies excluded as they did not solely look at the specifics of MDMA and PTSD. Multiple other studies were excluded as they dealt with specific populations, and several more were excluded as they duplicated data. Seventeen studies met the final criteria.

MESH terms: ("n methyl 3,4 methylenedioxyamphetamine"[MeSH Terms] OR "n methyl 3 4 methylenedioxyamphetamine"[All Fields] OR "mdma"[All Fields]) AND ("stress disorders, post traumatic"[MeSH Terms] OR ("stress"[All Fields] AND "disorders"[All Fields] AND "post traumatic"[All Fields]) OR "post-traumatic stress disorders"[All Fields] OR "ptsd"[All Fields])

Other keywords: PTSD, post-traumatic stress disorder, MDMA, 3, 4-methylenedioxymethamphetamine, history of PTSD, history of MDMA

Literature Review

PTSD Defined

Post-traumatic stress disorder (PTSD) is a common, chronic mental health condition that is triggered by exposure to a traumatic event. First recognized in the 1980s, PTSD was generally linked to Vietnam War veterans and thought to be a consequence of war, but researchers soon noticed similar disease patterns in individuals who had survived rape or sexual assault, ethnic cleansing, and natural disasters (Yehuda et al., 2015). Since the first recognition of a post traumatic syndrome, the definition of the disease has evolved into a commonly diagnosed illness. Symptoms of PTSD include distressing thoughts or emotions related to the event, nightmares, flashbacks, insomnia, hypervigilance, irritability, and emotional withdrawal. As a result of these symptoms, PTSD patients often avoid situations, people, or anything else that may serve as reminders of the incident, often leading to social isolation (U.S. Department of Veterans Affairs, n.d.). The combined effect of these symptoms leads PTSD patients to have an increase in co-conditions such as substance abuse, anxiety disorders, self-harm, and suicidal ideations as well as higher risks of medical comorbidities such as chronic pain, cardiometabolic disorders, and dementia (Yehuda et al., 2015).

PTSD Epidemiology

The American Psychiatric Association (APA) estimates that 1 of every 11 Americans will suffer from PTSD in their lifetime, with an annual prevalence of 3.5% of the population. Further research has found that the diagnosis is twice as common in women compared to men, and US Latinos, African Americans, and American Indians more commonly affected than Caucasian Americans (APA, 2020).

Additional research by the National Center for PTSD looked at the diagnosis in adolescents and found that children exposed to violence in their childhood were at a higher risk of developing PTSD later in life. Furthermore, rates of PTSD in children ages 12-17 were slightly higher than that of adults, with a 6-month prevalence of approximately 5%, affecting 3.7% of boys and 6.3% of girls (U.S. Department of Veterans Affairs, n.d.).

Research into the common cause of PTSD found the highest rates of diagnosis were among survivors of rape or sexual assault, childhood trauma, and military combat (Yehuda et al., 2015). Kelmendi et al. (2016) also found that nearly 20% of combat exposed military veterans had symptoms consistent with PTSD.

PTSD Etiology

PTSD is a rarity in the mental health arena, as it is one of the only psychiatric diagnoses in which the cause, a traumatic event, is known. Unfortunately, PTSD is a complex disease, involving neuroendocrine, neurochemical, and neuroanatomical pathology, and although it has been studied extensively, no definitive answer has been found as to why PTSD occurs (Kirkpatrick & Heller, 2014). It is estimated that 90% of individuals will be exposed to a traumatic event in their lifetime, yet only a fraction of those will go on to develop PTSD (Kirkpatrick & Heller, 2014). While there is no definitive reason for why a certain subset of the population fails to recover from the traumatic event, the National Center for PTSD outlines several neurological alterations that may play a role. Individuals living with PTSD may present with disruptions in psychophysiological processes, which may manifest as hyperarousal of the sympathetic nervous system; neuroendocrine abnormalities seen in alterations of noradrenergic, hypothalamic-pituitary-adrenal (HPA) axis, serotonergic, glutamatergic, thyroid, and opioid levels; structural brain disruptions, shown as decreased hippocampal and anterior cingulate mass;

and functional brain disturbances, seen as an increase in amygdala activity along with a decrease in prefrontal cortex (PFC) and hippocampus activity (U.S. Department of Veterans Affairs, n.d.).

Further hypotheses of the etiology of PTSD from Kirkpatrick and Heller (2014), discusses the concept of fear learning and how alterations in the amygdala, PFC, and hippocampus can interfere with the normal processes. The amygdala is commonly thought of as the fear center of the brain, and an increase in activity, as seen in PTSD, can cause an increase in fear-based symptoms. Contrarily, the PFC is responsible for cognition, reasoning, and thought control. In healthy individuals, the PFC acts as a moderator of the amygdala, but in those with PTSD, there is a decrease in PFC activity, leaving the amygdala without a balance. The hippocampus is responsible for storing and retrieving memories and is thought to have a role in recalling and associating safe memories to fearful stimuli. In PTSD patients, smaller hippocampal volumes have been documented, which may lead to an inability of the patient to reassociate safe memories to traumatic events (Kirkpatrick & Heller, 2014).

The symptoms of PTSD often cause patients to develop avoidance strategies to prevent exacerbation of symptoms, but this technique often leads to more harm than good. By limiting one's exposure to the triggering stimuli, there are fewer safe exposures to the trigger, preventing fear extinction strategies from overwriting the prior fear cues with safer ones and thus reinforcing the fear (Kirkpatrick & Heller, 2014)).

Current PTSD Therapies

Research into PTSD has found various interrelated neurotransmitter pathways that are thought to be responsible for the symptoms of the disease. Kelmendi et al. (2016) reviews several of these mechanisms implicated in PTSD and the targeted treatments for each of them.

Serotonin is thought to be a key player in PTSD, therefore much research has been done into selective serotonin receptor inhibition (SSRI) therapy. To date, only two medications, paroxetine and sertraline, have been granted FDA approval for the treatment of PTSD. Kelmendi et al. (2016) reviewed several articles that measured response rates of paroxetine vs placebo, as well as sertraline vs placebo, and found varying results. Kelmendi et al. cites two articles reviewing paroxetine, both of which showed superiority over placebo (Alexander, 2012, & Alexander, Lund, Bernardy, Christopher, & Friedman, 2015). Sertraline however, had varying results with two studies showing superiority over placebo (Brady 35 al., 2000, & Davidson, Rothbaum, van der Kolk, Sikes, & Farfel, 2001), and two others showing no significant differences in sertraline vs placebo (Zohar et al., 2002, & Benedek, Friedman, Zatzick, & Ursano, 2009). Interestingly, the latter two studies were limited to veterans in the VA hospital, whereas the previous studies were comprised of patients in the general population. This makes comparing the studies difficult as results may be due to confounding factors and differences in patient populations rather than the pharmacotherapy. Furthermore, very few studies were used, without consistency among them, making it difficult to evaluate and compare the data.

Another neurotransmitter Kelmendi et al. (2016) reviewed is the noradrenergic system and its role in hyperarousal, tachycardia, and anxiety. Chronic hyperadrenergic activity is thought to be responsible for the poor sleep and nightmares that many PTSD patients suffer from. One study analyzed by Kelmendi et al. (2016) looked at the use of Prazosin, an alpha-1-noradrenergic receptor blocker, in treating insomnia and nightmares. While the study was small, n=22, statistical significance was found in the treatment of these symptoms. Although again, the study was limited to veterans, and a small sample size, therefore it is questionable whether these results can be replicated and extrapolated to different populations (Kelmendi et al., 2016).

GABA was also reviewed as a potential pharmacotherapy target as alterations in the GABAergic system have been involved in PTSD as it has a part in both memory registration and fear encoding (Kelmendi et al., 2016). The medications of choice for this aspect have long been benzodiazepines, yet research from Kelmendi et al. (2016) found that while benzodiazepines are helpful for insomnia, their addiction potential in addition to their disruption of fear extinction and interference in effectiveness of exposure therapy, made them more of a hinderance to therapy then benefit. Other GABA agents, such as tiagabine and divalproex, have been researched, but no conclusive results have been found (Kelmendi et al., 2016).

The results of Kelmendi et al. (2016) research took an interesting approach and focused on specific treatments for specific aspects of PTSD symptoms. Unfortunately, the research presented failed to offer a reliable and well-supported treatment option for any of the targets of PTSD symptoms.

In the research on PTSD therapy, an area that is lacking considerable data is in head-to-head trials of pharmacotherapy vs psychotherapy. And while there are practice guidelines for PTSD therapy, and several comprehensive reviews of PTSD treatments, they all differ in scope, methods, and conclusions, leaving no clear stands for definitive treatment (Watts et al., 2013). A meta-analysis conducted by Watts et al., (2013), sought to address these gaps and bring together information to allow comparisons across treatments groups, giving providers the ability to make more informed decisions for their patients.

Watts et al., (2013) conducted a thorough meta-analysis covering 112 studies that contained data from 137 separate comparisons. The analysis divided treatments into three primary categories, psychotherapy, somatic treatments, and medications. Results of the analysis found that effect sizes for each of the 3 categories differed significantly from the control groups:

psychotherapy (g=1.14), somatic treatments (g=1.24), and pharmacotherapy (g=0.42). When comparing directly, psychotherapy had a larger effect size than medications (Z=1.10, P<.001), while somatic treatments did not differ significantly from psychotherapy or medications (Watts et al., 2013).

Further research into psychotherapy found the majority of comparisons included cognitive based therapy (CBT), comprising 72% of the studies. This subset also had the highest effect size (g=1.26). Eye movement desensitization was the next largest, and most effective, category (g=1.01). A single trial looking at resilience therapy had a large effect size (g=1.26), although the study has not been replicated. Additional psychotherapy methods, including hypnotherapy, psychodynamic psychotherapy, group psychotherapy, biofeedback, and self-help/self-guided therapy, didn't include definitive data to recommend their use (Watts et al., 2013).

Forty-four studies were evaluated in the medication category, 32 comparing SSRIs, 9 comparing atypical antipsychotics, and 3 assessing anticonvulsant use. The antidepressant group had the largest effect size (g=.43), with the range of SSRIs varying widely from significant effects of paroxetine (g=0.74), fluoxetine (g=0.43), and sertraline (g=0.41), to potentially negative effects of citalopram (g=-0.71). In the atypical antipsychotic category, only Risperidone showed potential use, although studies varied in effect size from g=0.31 to g=0.95. Topiramate was the only anticonvulsant that differed significantly from placebo, with effect sizes ranging from g=0.85 to g=1.84 (Watts et al., 2013).

A notable finding in both the psychotherapy and pharmacotherapy studies was studies with more women had more significant effects, whereas studies with more veterans had smaller effect sizes. This result is similar to the results of Kelmendi et al. (2016) in which results of

Sertraline differed between PTSD sufferers in the general population versus veterans (Watts et al., 2013).

The authors of the meta-analysis noted several limitations and potential areas of bias. Most notably is the possibility of publication bias, with positive studies being more likely to be published than if results were negative. Further limitations include the heterogeneity of treatments between studies, which could have influenced study results. The last finding, and perhaps the most interesting, in both pharmacotherapy and psychotherapy, was studies involving more women had larger effect sizes while those with more veterans had smaller effect sizes. This finding is consistent with the data from Kelmendi et al., where sertraline was more effective in the general population groups than in the veteran's groups. While other confounding factors may play a role, more research is needed to determine whether gender or veteran status play a role in treatment outcomes (Watts et al., 2013).

Current clinical practice guidelines (CPGs) for PTSD fail to offer providers clear treatment guidelines for patients. Furthermore, contradictory recommendations are given from the top agencies on which method is preferred. The Veteran's Affairs/Department of Defense (VA/DoD), APA, and International Society for Traumatic Stress Studies (ISTSS) have stated support for both pharmacotherapy and psychotherapy as first line options. Contrarily, the National Institute for Clinical Excellence (NICE) and the World Health Organization (WHO) have advocated for trauma-focused psychotherapy (TFP) as first line treatment, and actually recommend against pharmacotherapy if psychotherapy is available (Lee et al., 2016).

Another hurdle clinicians face is the lack of consensus on which class, or medication within a class, are best for PTSD patients. The VA/DoD has concluded all SSRIs and SNRIs are equally as effective for first line treatments, whereas the ISTSS have only recommended

sertraline, paroxetine, fluoxetine, and venlafaxine for first line treatment. In addition, the ISTSS recommends mirtazapine, nefazodone, and prazosin as first line treatments as well. The APA only recommends SSRIs as first line options and the WHO only recommends TCAs and MAOIs (Lee et al., 2016).

A series of meta-analyses by Lee et al. (2016) sought to address these issues and provide more information on whether TFPs are superior to medications, as well as deciphering which medications may be most effective. A total of 55 studies were included, comprising 6,313 total participants. Intervention studies included aripiprazole, brofaromine, bupropion, trauma-focused cognitive behavioral therapy (TF-CBT), citalopram, divalproex, eye movement desensitization and reprocessing (EMDR), fluoxetine, guanfacine, interpersonal therapy (IPT), mirtazapine, nefazodone, olanzapine, paroxetine, prolonged exposure therapy (PE), prazosin, risperidone, sertraline, stress inoculation therapy (SIT) tiagabine, topiramate, and venlafaxine (Lee et al., 2016).

Results of the study found that TFPs were the superior treatment option, outperforming all other psychotherapies and pharmacotherapies. Significant effect sizes were noted for TFPs, and large reductions were noted in clinician administered PTSD scale (CAPS) scores that persisted long after therapy had been completed. Of the medications evaluated, only sertraline, venlafaxine, and nefazodone were found to have statistically significant effect sizes; all others assessed never achieved significance over the control groups. In addition, the authors of the study found that medication use was required for long-term benefits, suggesting pharmacotherapy merely blunts PTSD symptoms, rather than resolving them (Lee et al., 2016).

Limitations of this study included difficulty in comparing studies with differing designs, publication bias, studies with small sample sizes, and several studies with lack of follow-up.

Furthermore, psychotherapy is a difficult treatment to assess and extrapolate as the therapy is very much therapist dependent and will vary substantially from practice to practice (Lee et al., 2016).

Selective serotonin reuptake inhibitors (SSRIs) are the primary class of medications used in the treatment of PTSD, yet only about half of patients respond, with less than a fifth achieving full remission of symptoms (Berger et al., 2009). In the likely event that a patient doesn't achieve success with SSRIs, providers are left with no clear guidance on what second, or even third, line medications are most effective (Berger et al., 2009).

Berger et al. (2009) conducted a systematic review to provide clinicians with additional information on the best pharmacological interventions for their patients if SSRIs fail them. The major classes covered in this review consisted of antipsychotics, anticonvulsants, adrenergic-inhibitors, opioid antagonists, and benzodiazepines. A total of sixty-three, double-blind placebo-controlled studies were used for the article (Berger et al., 2009).

The first class of medications covered were antipsychotics. Antipsychotics are thought to work against PTSD symptoms by acting on several systems, including the serotonergic and dopaminergic systems, by binding to alpha-adrenergic receptors, as well as having antihistamine effects, which may aid in sleep disorders and insomnia symptoms. Six randomized control studies (RCT) were used investigating the efficacy of risperidone, with varying results. One showed superiority of risperidone over placebo with use as monotherapy, and three studies showed significance as risperidone used as adjunctive therapy. Two of the studies found no superiority of risperidone over placebo. None of the studies found that risperidone alleviated avoidant behavior or emotional numbness in PTSD sufferers. Olanzapine was a second antipsychotic studied, yet only two RCTs were found, with conflicting results. One study utilized

the CAPS criteria and found a significant decrease in patients treated with olanzapine, while another study utilized different measurement outcomes, and found no statistical differences among treatment and placebo groups. Several other antipsychotics were reviewed, including quetiapine, clozapine, and aripiprazole, although no RCTs were found comparing them to placebos, therefore evidence of efficacy of these medications was limited to levels C or D (Berger et al., 2009).

Anticonvulsants are another class of medication that has been thought to have use in PTSD due to their anti-kindling effects as well as their ability to enhance GABAergic and serotonergic neurotransmission and inhibition of glutamatergic neurotransmission. Of the anticonvulsants studied, valproic acid, lamotrigine, carbamazepine, topiramate, tiagabine, levetiracetam, phenytoin, gabapentin and vigabatrin, only one, lamotrigine, had a RCT with statistical significance, although the study size was small, only consisting of 14 patients. Valproate was found to have several open label studies, with varying results (Berger et al., 2009).

The only adrenergic-inhibiting agent found to have any benefit was Prazosin. Three RCTs found that prazosin significantly increased sleep time and decrease in PTSD related nightmares, with two of the studies finding statistical significance in decrease of CAPS scores. Propranolol and clonidine were both studied with open label studies and seemed to show a decrease in intrusive thoughts and hyper arousal symptoms, yet none of the studies provided a control group. One RCT was found evaluating guanfacine, with no superiority over placebo for any of the PTSD symptoms and was actually found to have detrimental side effects (Berger et al., 2009).

There has been interest in opioid antagonist treatment for PTSD patients after research has shown an increase in opioid activity among individuals suffering from PTSD. Two open label studies were found, one each evaluating nalmefene and naltrexone. Eight out of eighteen patients reported improvements using nalmefene, while no patients saw a decrease of symptoms with naltrexone. Additionally, all patients in the naltrexone group reported early side effects with limiting the dosage used (Berger et al., 2009).

Benzodiazepines are a class of medications commonly thought to be helpful in PTSD due to their effect on GABAergic transmission and inhibition of the amygdala. One RCT and one open label study were found evaluating alprazolam, with neither showing any benefit of PTSD symptoms. One open label study was found assessing temazepam, which showed an improvement of sleep, but no reduction in PTSD symptoms were found (Berger et al., 2009).

In summary, results of the review found that no medications, other than SSRIs, found level A evidence for treatment against PTSD symptoms. Five medications, risperidone, olanzapine, lamotrigine, valproate, and prazosin achieved level B evidence, with all of the others evaluated warranting either level C or D recommendations (Berger et al., 2009).

Limitations of this review are similar to those presented prior, including publication bias as well as the inclusion of combat veterans, who are notoriously refractory to conventional treatment. In addition, many of the studies did not offer information on whether the pharmacotherapy being evaluated were employed as a monotherapy or in tandem with other agents. Lastly, heterogeneity in studies and differences in evaluation criteria make comparing studies and study results difficult (Berger et al., 2009).

What is MDMA

In 1913, a new diet drug, 3,4-Methylenedioxymethamphetamine (MDMA), a member of the methamphetamine family, hit the market from Merck pharmaceuticals (Jenkins, 2020). While MDMA never took off for its intended purpose, it found a new niche among psychedelic therapists after LSD was banned in the late 1960s (National Institute of Health, 2017). Throughout the 1970s, several therapists began experiments with MDMA and found that it was able to elicit feelings of empathy and bonding as well as increasing willingness to talk about emotional memories, thereby allowing patients to retrieve and reprocess the memories associated with the PTSD (National Institute of Health, 2017). It didn't take long before MDMA found its way into the party scene, where it became known as Ecstasy, or simply as E. In 1985, Ronald Regan's FDA had an emergency meeting regarding the newest party drug, and subsequently added MDMA to the list of Schedule I medications, halting any potential research into its therapeutic effects (Sessa, Higbed, & Nutt, 2019).

There are several ways in which MDMA appears to aid in the treatment of PTSD. First, MDMA enhances the release of monoamines such as serotonin, dopamine, and noradrenaline. Increased levels of serotonin have been shown to reduce feelings of depression and anxiety, as well as moderating the amygdala's fear response and increasing one's self-confidence. Increased levels of dopamine and adrenaline are thought to have positive effects on awareness and arousal, possibly motivating engagement in therapy as well as helping in fear extinction. Second, MDMA enhances the release of oxytocin which can increase levels of empathy and bonding while also playing a role in moderating the fear response of the amygdala. Lastly, MDMA may act on alpha 2 receptors, causing relaxation and sedation, offsetting the hypervigilance brought on by PTSD.

Furthermore, MDMA may increase communication between the amygdala and hippocampus and as a result, allow for reprocessing of traumatic memories (Sessa, Higbed, & Nutt, 2019).

Psychologists and researchers alike believe that MDMA has a unique ability to dampen the fear response while leaving other functions intact, allowing the patient to access prior traumatic memories and reprocess them. Unlike other medications that merely dampen PTSD symptoms, MDMA has the potential to reprogram the fear pathways created by PTSD, facilitating a healing process (Sessa, Higbed, & Nutt, 2019).

The limited research that had been carried out in the 1970s on MDMA and PTSD had shown promising results, and several members from across psychological fields were convinced MDMA could be the key to treating several mental health disorders. In 1986, psychedelic psychotherapist Rick Doblin launched a nonprofit organization called the Multidisciplinary Association for Psychedelic Studies (MAPS) (Emerson, et al., 2014). The mission of MAPS was to advocate for further research into the use of psychedelics, primarily MDMA, as a therapeutic adjunct in several mental health disorders. While it has taken 25 years, MAPS is currently wrapping up the first double-blind, placebo-controlled trial of MDMA-assisted psychotherapy for PTSD. It is expected that the results of this trial will lead to FDA approval of MDMA for use in PTSD by early 2022 (Emerson, et al., 2014).

Current MDMA Research

Due to its designation as a Schedule I medication, research on the use of MDMA has been limited. All studies published have been performed under the MAPS program, therefore study design has been consistent across clinical studies. The treatments to date have been set up as three 90-minute preparatory sessions, followed by three 8-hour MDMA sessions, spaced a

month apart, each followed by three 90-minute therapy sessions, one the morning after and two more prior to the next MDMA session. The therapists work in a co-therapy team of one female and one male, utilizing a non-directive setting to enhance a feeling of safety and support. The MDMA sessions themselves utilize eyeshades and music, with the patient talking about issues as they arise, only being prompted or redirected if a therapist feels it is necessary (Bahji et al., 2020) . MDMA doses ranged from 75-125mg in the experimental group and small doses (0-40mg) were administered in the control group to elicit a small response in an effort to maintain the blinding of participants (Jerome, et al., 2020).

The first controlled clinical study for MDMA assisted psychotherapy was published in 2010. Twenty patients with treatment resistant PTSD underwent nondrug psychotherapy and then either inactive placebo or two or three sessions of MDMA therapy. At both two and twelve month follow ups, 83% of MDMA groups no longer met criteria for PTSD, compared to just 25% with the placebo group. Remission was maintained for up to 6 years (Sessa, Higbed, & Nutt, 2019).

Following the results of the above studies, six phase 2 trials took place, enrolling 103 participants. Comparison of CAPS scores at the end of the trials found that 52.7% of the experimental group no longer met criteria for PTSD compared to only 22.6% of those in the control group. As a result of these studies, the FDA granted breakthrough therapy designation, allowing phase 3 trials to be conducted (Fedducia & Mithoefer, 2018). .

Several phase 3 trials are currently underway, and results of the first were released in May 2021. The study consisted of 92 participants, from 15 different sites across the United States, Canada, and Israel. Results found that MDMA produced statistically significant reductions in CAPS scores of patients ($p<0.0001$, $d=0.91$) as well a decrease in Sheehan

Disability Scale (SDS) scores (p=0.0016, d=0.43). Adverse reactions, to include suicidality, abuse potential, and QT prolongation were monitored and found no difference between the two groups. Furthermore, MDMA was equally effective in patients with comorbidities that are typically resistant to treatment, such as veterans (Mitchell et al., 2021). Several limitations of this study should be noted. First, the number of participants is smaller than the authors had planned due to Covid-19. A larger subject population would be more ideal, although the statistical significance of results is still convincing. Second, the authors noted a lack of both racial and ethnic diversity, both of which should be addressed in future studies. Third, is the resulting of data only 5 weeks after the completion of the trial. Additional information will be necessary to evaluate the long-term results of MDMA treatment. Lastly, due to the psychological effects of MDMA, it is challenging to conduct a truly blind study. Interestingly though, several patients in both groups (7 of 44 in the placebo and 2 of 46 in the experimental group) believed they were part of the other group (Mitchell et al., 2021).

MDMA Safety

While the data on MDMA treatment of PTSD looks promising, it is important to remember that MDMA is a Schedule I drug and a member of the methamphetamine family with several potential side effects. Acute adverse effects of MDMA, although rare, include hypertension, fainting, panic attacks, loss of consciousness, and seizures. One of the most serious effects of MDMA is its ability to interfere with the body's thermoregulatory system, causing a marked rise in body temperature, necessitating emergent treatment before muscle breakdown, electrolyte imbalances, or kidney failure results. Less severe, but more common, side effects include jaw clenching, lack of appetite, depersonalization, disorganized thoughts, restless legs,

nausea, hot flashes, chills, headache, sweating, and muscle or joint stiffness (National Institute of Health, 2017).

While the MAPS study design only consists of 3 treatments, repeated or regular use of MDMA has been linked to several problems including insomnia, concentration difficulties, depression, heart disease and a decrease in cognitive function. In addition, the MOA that makes MDMA likely beneficial in PTSD is its effects on serotonin and norepinephrine, can have deleterious effects as well. Large doses of MDMA can deplete the serotonin stores of the body, causing the body to be serotonin deficient for several days after treatment, leading to depression, anxiety, and possible suicidal ideations. Studies have shown that moderate to high doses of MDMA given twice a day for 4 days can significantly reduce the number of serotonergic neurons, indicating that MDMA use may have significant long-term effects (Thal & Lommen, 2018).

It is important to note that while the clinical studies involving MDMA have been small, none of these side effects have been noted.

Discussion

In summary, this literature review presents evidence that MDMA assisted psychotherapy has the potential to be an effective, durable, and safe treatment option for patients with chronic, relapsing, and refractory PTSD. Results of the first phase 3 randomized control trial published in May 2021 showed that participants (n=90) in the MDMA treatment group showed a statistically significant decrease in both CAPS and SDS scores ($p < 0.0001$ and $p=0.0116$ respectively). In addition, while MDMA was placed on the class I controlled substance list due to concerns of

adverse effects, no deleterious effects, nor abuse potential, was noted in the control group. While these results look promising, much research still needs to be done on the efficacy, safety, and longevity in larger populations.

The use of novel drugs in the treatment of mental health disorders is a promising and exciting new arena in medicine. In addition to MDMA, there is ongoing research into the use of other psychoactive substances such as psilocybin, marijuana, ayahuasca, and lysergic acid diethylamide (LSD) in the treatment of PTSD, as well as anxiety and depression. These drugs offer the ability to alter neuronal pathways, potentially curing these diseases as opposed to simply masking the symptoms. Unfortunately, these drugs tend to conjure negative connotations in society, causing many challenges in research. As Byock states though, "we must not allow preconceptions, politics, or puritanism to prevent suffering people…from receiving promising, at times life-saving, treatments."

Applicability to Clinical Practice

PTSD is a common mental health disorder that causes a significant decrease in quality of life for those it affects. Current guidelines for treatment are vague and conflicting, leaving clinicians without definitive direction on therapeutic options. Furthermore, treatment options are often subtherapeutic, leaving clinicians and patients with few options. With the information presented in this literature review, I hope to outline research on current treatment options, as well as highlight the potential use of MDMA for PTSD sufferers who are resistant to the current therapies available.

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