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The Promise of MDMA in the Treatment of Severe Post-Traumatic Stress Disorder

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ABSTRACT

Post-traumatic stress disorder (PTSD) is an often debilitating condition caused by a person's exposure to traumatic events. Symptoms of PTSD include intrusive thoughts, suicidal ideation, and highly negative and distressing emotional states. Current treatments for PTSD such as cognitive behavioral therapy, EMDR, and SSRIs and SNRIs are ineffective for a large chunk of patients who seek out treatment. A majority of patients with PTSD do not respond to talking therapy, and the remission rate for patients on SSRIs and SNRIs is low. The ineffectiveness of recommended treatments has led to experimentation with drugs like MDMA. MDMA increases levels of chemicals in the brain that induce happy and calm states. This drug also decreases fear states in patients, allowing them to more comfortably discuss traumatic events without the possible side effects of extreme emotional numbness or high levels of anxiety. Research conducted in the last decade on MDMA in addition to psychotherapy in a clinical setting has yielded impressive results. A majority of patients in all three conducted trials experienced a long-term reduction in PTSD symptoms. MDMA in a clinical setting was also proven to be safe, with no serious drug-related side effects on patients. With such high rates of symptom reduction, these studies provide hope for the future of effective and safe PTSD treatment.

Introduction

"Psychedelics" is an umbrella term for compounds such as lysergic acid diethylamide (LSD), psilocybin, mescaline, MDMA, and other substances that alter an individual's perception of themselves and their ability to mentally process their surroundings (Belouin and Henningfield, 2018). The drugs' rise in popularity and association with counter-culture movements during the 60s led to the adoption of the term psychedelic (Belouin and Henningfield, 2018). This political association also led to their stigmatization as tragic incidents associated with the drugs became national topics of discussion and led to a conservative push for regulation (Carhart-Harris et al., 2018). These compounds were classified as Schedule I drugs in 1967 by the United Nations, which meant that they were considered to have no application medically and have significant potential for harm and dependence (Nutt, 2019). Additionally, the 1970 US Controlled Substances Act imposed penalties on the usage, distribution and manufacturing of psychedelics (Belouin and Henningfield, 2018). These actions essentially shut down research on the drugs for 40 years (Nutt, 2019).

However, scientific efforts in the last decade have sought to redefine our perception of these drugs as wholly harmful and instead as useful in treating psychiatric disorders such as anxiety, clinical depression, schizophrenia, and post-traumatic stress disorder. One of these drugs, MDMA, the abbreviation of 3,4-methylenedioxy-N-methylamphetamine, is considered both a stimulant and a psychedelic. It was declared as a Schedule I drug in the United States in 1985, and was used before then as an addition to psychotherapy for its reported effect of decreased fear and more focused states (Mithoefer et al., 2010). Recent trials on MDMA in conjunction with psychotherapy provide hope for the usage of MDMA to help patients with severe PTSD.

Post-Traumatic Stress Disorder Symptoms and Treatment

Post-traumatic stress disorder (PTSD) is a condition developed after exposure to a singular traumatic event or long-term trauma that causes an alteration in behavior and symptoms that affects a person's daily life (Feduccia and Mithoefer, 2018). Symptoms of PTSD include intrusive memories and dreams, dissociative reactions, alterations in reactivity, negative alterations to mood and cognition, avoidance of trauma-related situations, and suicidal behavior (Schrader and Ross, 2021). The current main recommended treatment method for PTSD is trauma-focused psychotherapy, which includes exposure therapy and cognitive behavioral therapy (Schrader and Ross, 2021). 40-60% of patients, however, also do not exhibit preferred results because this therapy relies on using trauma-related cues or the discussion of traumatic events that can cause a patient to be unable to complete a session due to emotional distress (Feduccia and Mithoefer, 2018). Additionally, this can be ineffective to patients with emotional detachment and loss or fragmentation of their trauma-related memories, like those who experience dissociation (Feduccia and Mithoefer, 2018). Eye Movement Desensitization and Reprocessing (EMDR), another form of treatment, works by talking through events with a patient while moving their eyes in a certain way, and can be useful to patients but is affected by symptoms like dissociation (Mithoefer et al., 2010). Another treatment option, often in conjunction with therapy-based treatment, is medication like antidepressants. The two kinds of antidepressants approved by the Food and Drug Association (FDA) for the treatment of PTSD are selective serotonin inhibitors (SSRIs) and norepinephrine reuptake inhibitors (SNRIs). SSRIs, like Sertraline and Paroxetine, can be effective, but the response rate to this drug for patients being treated is only 60% (Berger et al., 2009). Out of this 60%, only 20-30% of patients actually achieve full remission (Berger et al., 2009). The effectiveness of SNRIs, mainly the drug Venlafaxine that is often used to treat PTSD, varies, with remission rates similar to that of Sertraline and peaking at 50% in one study (Berger et al., 2009). Other drugs, like atypical antipsychotic agents, have been studied as a treatment but all result in remission rates that vary little from the effectiveness of SSRIs (Berger et al., 2009). SSRIs also have a variety of side effects, like an increase in suicidal thoughts and dangerous interactions with other medicines, and it can take a long time for a patient to see if a certain medication works for them and if they need to try another (Cautions, n.d.). Generally, current therapies are only effective for 25-50% of patients (Mithoefer et al., 2010). Due to these reasons, the search for new, effective medicine has been prominent, especially with the backdrop of a global mental health epidemic.

MDMA has multiple effects on its users, like increased levels of serotonin, dopamine, and norepinephrine that results in happiness and calmness (Feduccia and Mithoefer, 2018). Increasing activity in the prefrontal cortex, MDMA, as a mild hallucinogenic and major mood elevator, causes positive and social behavior and has been shown to facilitate fear extinction (Young et al., 2015). This means that the drug, when tested on animals, alleviated habits of conditioned freezing in traumatic situations, even in multiple different environments (Young et al., 2015). The idea behind using MDMA as an addition to psychotherapy is based on MDMA's reduction of exaggerated fear responses associated with PTSD, therefore making it helpful to patients with chronic, treatment-resistant PTSD (Mithoefer et al., 2010). Essentially, a person given MDMA in a trial can find a long-lasting balance between extreme emotional numbness and overwhelming anxiety due to the mood-elevating effects of the drug that results in effective exposure therapy (Mithoefer et al., 2010).

Studies on the Usage of MDMA in PTSD Treatment

The first completed pilot study on MDMA's usage in PTSD trials was published in 2010 (Mithoefer et al., 2010). This study involved 20 subjects at the mean age of 40.4 years, with 19+ years as the estimated average duration of PTSD each subject experienced (Mithoefer et al., 2010). All subjects experienced treatment-resistant PTSD, with the qualifications being a CAPS score of greater than 50 after at least 3 months of SSRI or SNRI

treatment and 6 months of psychotherapy (Mithoefer et al., 2010). The CAPS (Clinical Administrated PTSD Scale) is a test based on the DSM IV that assesses PTSD symptoms and makes PTSD diagnoses (Weathers et al., 2013). Subjects were randomized in double-blind test, with both groups receiving psychotherapy but one with a placebo pill (8 people) and the other with MDMA (12 people) (Mithoefer et al., 2010). In the experiment, subjects stayed at an outpatient facility and partook in 8 integration sessions for additional emotional processing after experimentational sessions in which they took either the placebo or MDMA pill, a process that is repeated in studies continuing after phase I (Mithoefer et al., 2010). These experimental sessions consisted of a pill taken in the morning, either placebo or containing 125 mg of MDMA, after which subjects had periods of conversation that focused on introspection and therapeutic discussion (Mithoefer et al., 2010). The 125 mg of MDMA, although still low, is higher than in sparse preliminary studies, such as one incomplete study published in 2008 that showed positive results in women with PTSD taking between 50 and 75 mg, an amount determined safe (Bouso et al., 2008). Subjects in the 2010 study could also take an optional additional dose, with consent and monitoring by professionals, of 62.5 mg of MDMA or placebo (Mithoefer et al., 2010). This was a 2-stage study, with the baseline that subjects had similar CAPS scores at the beginning of the trial (Mithoefer et al., 2010).

The results of the study in showed that the usage of MDMA resulted in significant symptom reduction, with a high percentage of subjects no longer meeting the criteria for PTSD on the CAPS scale after only 2 months of MDMA-assisted psychotherapy (Mithoefer et al., 2010). Specifically, 10 out of the group of 12 (82%) receiving MDMA alongside psychotherapy were completely off the CAPS scale for PTSD symptoms, meaning they no longer qualified for diagnosed PTSD (Mithoefer et al., 2010). In the second stage, 7 subjects chose to repeat the study but with an open-label crossover (Mithoefer et al., 2010). This yielded a 100% clinical response rate, with 6 who had not responded to the placebo and all three subjects who had reported being unable to go to work due to PTSD able to return to work (Mithoefer et al., 2010). Additionally, all patients received follow up psychotherapy.

One drawback of the MDMA pills is that some patients experienced some physical side-effects, like nausea, insomnia, and loss of appetite, but these usually resolved quickly, with the longest period being a few days (Mithoefer et al., 2010). Notably, side effects from current recommended medications can last much longer and be more severe (like increased suicidal thoughts or the possibility of serotonin syndrome), and there were no serious drug-related effects in the study (Mithoefer et al., 2010). In comparison with current recommended medication, the number of patients who achieved remission, and the improvement of CAPS scores in general, considerably outnumbers averages for patients who take SSRIs or SNRIs.

A second trial with the same topic was conducted in 2012 (Oehen et al., 2012). This trial, consisting of 12 subjects, administered a dose of 125 mg, followed up by 12.5 mg of MDMA 2.5 hours later, and an active placebo dose of 25 mg followed by 12.5 mg (Oehen et al., 2012). The important conclusion from the second trial is that these doses of MDMA, which are much higher than earlier experiments, is safe to use in clinical environments with no adverse drug-related effects (Oehen et al., 2012). Three experimental sessions dosing MDMA were more effective than two, and still contained no dangerous health effects for participants (Oehen et al., 2012). One difference in this trial as compared to the first is that participants were evaluated one year after the experiment, and patients displayed statistically and clinically significant decreases in CAPS and self-reported improvement scores (Oehen et al., 2012). However, this second trial showed no statistically significant improvements on the CAPS scale (not self-reported scores, which did show a statistical improvement) in the short-term, but results only narrowly missed statistical significance (Oehen et al., 2012). Despite this, a total analysis of 6 phase II trials short-term results on average showed a 44.8-point decrease in CAPS scores upon exit from treatments, ranging from 1-2 months, with doses ranging from 75-125 mg of MDMA (Jerome et al., 2020). Immediate treatment exit caused 56.0% of patients to no longer met PTSD criteria, a percent that increased to 67.0% after long-term follow up (Jerome et al., 2020). Remission is strongly durable, with long-term symptom reduction at 3.5 years after treatment (Jerome et al., 2020).

With the success of phase II trials, MDMA-assisted psychotherapy was designated as a Breakthrough Therapy in 2018 (Feduccia and Mithoefer, 2018). A phase III trial was published in 2021. The average length of PTSD diagnosis in this trial was 14.8 years for the MDMA group and 13.2 years in the placebo group (Mitchell et al., 2021). Notably, 18 total participants also had a dissociative subtype, which can decrease the effectiveness of current therapeutic treatment (Mitchell et al., 2021). After 18 weeks of treatment, 67% of patients in the MDMA group no longer met criteria for PTSD (Mitchell et al., 2021). Much like previous trials, some patients experienced side effects, but no patients had adverse events related to suicidality (Mitchell et al., 2021). Participants with the dissociative subtype experienced roughly the same decreases in CAPS scores as the rest of participants in the MDMA group (Mitchell et al., 2021). The overall mean change in CAPS score was -24.4 points for the MDMA group (Mitchell et al., 2021).

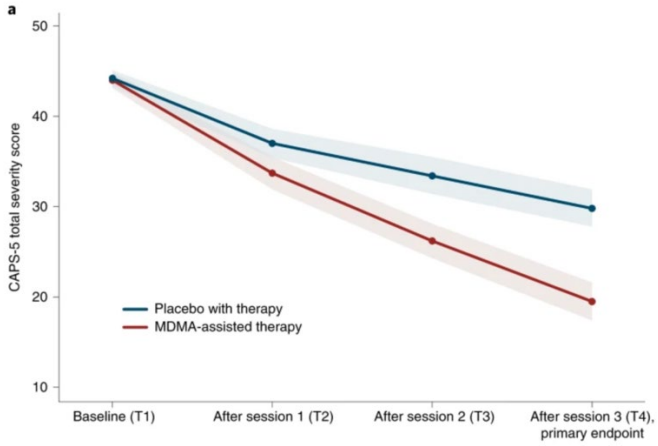

Figure 1. The mean decreases in CAPS scores for the placebo and MDMA groups (2021).

Is Using MDMA as a Treatment Safe?

Ethical and safety concerns around the usage of MDMA exist. Certainly, MDMA can be psychologically addictive. Some people who use MDMA report habits of substance abuse, such as cravings, withdrawal, and continual use despite consequences (Is MDMA addictive, 2021). Testing on animals shows that they will self-administer the drug, a sign of addiction potential (Is MDMA addictive, 2021). Additionally, all trials on MDMA did result in different types of side effects for some participants, like higher body temperature and nausea.

The argument for the usage of psychedelics is first and foremost informed by the success of pilot studies. With such a high rate of participants no longer meeting the qualifications for PTSD in one MDMA trial after just two months, this provides the future possibility for treatment that can be more beneficial for many people compared to current treatments. SSRIs and SNRIs do not work for many patients, and can cause a variety of unpleasant, and sometimes life threatening, side effects. The search for medication that works for a patient can be lengthy, with SSRIs taking on average 2 to 4 weeks to see benefits and 4 to 6 weeks to determine whether the drug is suitable for a patient (Cautions, n.d.). The time it takes for MDMA treatments to reduce or entirely eliminate symptoms is short compared to current medication, and with the possibility of current medications used losing their effectiveness, the 3.5-year average for symptom reduction with the usage of MDMA is particularly impressive. Additionally, MDMA trials showed no increases in suicidal ideation, which can be a side effect of current medication recommended for the treatment of PTSD. As a whole, the negative side effects reported in experimental trials on MDMA were short-lived and resolved by the end of the trials.

Additionally, research on the addictiveness of MDMA on a chemical level is inconclusive, with studies on dependence to the drug widely varying in results (Is MDMA addictive, 2021). A 2019 study on mice found, however, that non-chronic use of the drug in mice did not yield addictive results (Goldman, 2019). The phase III trial also showed no effects of abuse potential in a clinical setting (Mitchell et al., 2021). Both the 2010 and 2012 studies on PTSD involving MDMA had no serious adverse events occur due to the MDMA administered, leading to a conclusion by researchers in the second study that MDMA can be safely administered in a clinical setting with psychotherapy (Oehen et al. 2012). Notably, the studies on MDMA and PTSD also included rescue medications, like Zolpidem and benzodiazepines in the 2010 study, that were readily available in the case of medical emergencies caused by the consumption of MDMA (Mithoefer et al., 2010). When approaching the future of PTSD treatment, careful consideration and safe use within clinical settings is key. But with the immense potential MDMA has shown to have in alleviating PTSD symptoms, this drug should be considered and studied as a possible option for future patients seeking treatment.

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