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The Psychopharmacology of ±3,4 Methylenedioxymethamphetamine and its Role in the Treatment of Posttraumatic Stress Disorder

Timothy Amoroso, B.S.

Abstract—Prior to 1985, ± 3,4-methylenedioxymethamphetamine (MDMA) was readily used as a psychotherapeutic adjunct. As MDMA became popular in treating various psychiatric illnesses by mental health professionals, the public started to abuse the MDMA-containing recreational drug "ecstasy." This alarmed the DEA, which led to emergency scheduling of MDMA as a Schedule I drug. Due to its scheduling in 1985, human research and clinical use has been limited. The majority of research on MDMA has been focused on the drug's potential harmful effects rather than its possible therapeutic effects. The limitations on retrospective human studies and preclinical animal models of MDMA neurotoxicity are examined in this analysis. New research has shown that MDMA, used as a catalyst in psychotherapy, is effective in treating posttraumatic stress disorder (PTSD). This review also examines the psychopharmacological basis for the efficacy of MDMA-assisted psychotherapy. Specifically, the brain regions involved with both PTSD and those activated by MDMA (i.e., amygdala, anterior cingulate cortex, and hippocampus) are examined. Also, the possible neurochemical mechanisms involved in MDMA's efficacy in treating PTSD are reviewed.

Keywords— MDMA, MDMA-assisted psychotherapy, posttraumatic stress disorder, PTSD

±3,4-methylenedioxymethamphetamine (MDMA) was originally synthesized in 1912 by Merck as an intermediate for a drug designed to stop bleeding. From 1912 to the mid-1970s, MDMA was not well known or studied scientifically. David Nichols and Alexander Shulgin were the first biochemists to study the psychoactive properties of the drug in humans. In the first clinical study of MDMA, the two researchers found that the drug produced "an easily controlled altered state of consciousness with emotional and sensual overtones" (Shulgin and Nichols 1978). At that point, Shulgin suggested to a group of psychiatrists that the drug might have a therapeutic potential in treating mental disorders. Leo Zeff was the first noted psychologist to use MDMA as an adjunct to psychotherapy and found impressive results prior to any controlled clinical trials (Pentney 2001). By the 1980s, at least 150 therapists were using MDMA in their practice and an estimated 500,000 therapy and personal growth sessions had been conducted using MDMA as a therapeutic catalyst (Stolaroff 1997; Rosenbaum and Doblin 1991). Unfortunately, just as the drug was becoming well known in the clinical sphere, it was also being used recreationally under the name "ecstasy." In 1985, the Drug Enforcement Administration decided to emergency schedule MDMA

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and categorized it as a Schedule I drug. This legislation caused all clinical research to be terminated or severely restricted while the illicit use of the drug continued and, in some years, increased (Sessa and Nutt 2007). Also, the therapists that were using MDMA in their practices were either forced to discontinue using the drug with their clients or ignore the law and risk legal punishment.

In the mid-1990s, the majority of research done on MDMA was focused on the potential dangers of the drug. Many studies found that MDMA had neurotoxic effects in animal models and in human retrospective studies. However, some of the erroneous beliefs about MDMA revolve around flawed studies. For instance, George Ricaurte of Johns Hopkins University published a paper showing that MDMA produced severe dopaminergic neurotoxicity and death in primates. This paper was questioned because it estimated that nearly a million people every weekend use MDMA with a very low rate of complications (Mithoefer, Jerome, and Doblin 2003). Ricaurte's paper was later retracted from *Science* because it was found that methamphetamine was used in the experiment rather than MDMA as reported (Ricaurte et al. 2002). Although there are risks involved with the use of any drug, this article will not focus on the potential risks of MDMA use. The Food and Drug Administration has already concluded that MDMA has an acceptable risk to benefit ratio in a clinical setting (Doblin 2002).

This article will highlight the clinical use of MDMA. Specifically, it will review the subjective effects of the drug and the receptors responsible for those effects, the neuroanatomical regions of the brain that are activated by MDMA, and how the psychopharmacology of MDMA is linked to its efficacy in treating people with posttraumatic stress disorder. However, because there is still ongoing debate in the literature about the safety and efficacy of MDMA, the limitations of current human and animal research will also be discussed.

A NOTE ON THE INTERPRETATION OF COGNITIVE DEFICITS IN MDMA USERS

Since there is debate about the safety of MDMA, it may be necessary to mention some of the shortcomings of these findings. Andrew Parrott (2013) has written extensively on the neurocognitive effects produced by ecstasy, which include: deficits in retrospective memory, higher cognition, reduced serotonin transporter levels in the cerebral cortex, disturbed sleep architecture, and other behavioral and psychiatric problems. However, most of the studies exploring these effects on humans should be read with caution because they have many methodological flaws. For example, most employ non-randomized and retrospective methodologies, which have inherent biases. Also, it is difficult to control for poly-drug use, drug dose and purity, as well as preexisting or underlying mental disorders. An important issue is that there is often a selection bias when recruiting participants because heavy drug users from the rave culture are typically invited to participate in these studies. For example, Schilt et al. (2008) conducted a study measuring the cognitive deficits caused by ecstasy use in participants that had an average lifetime exposure of 327 tablets (range: 15–2000), while only 20–30% of ecstasy users consume more than 25 tablets in their lifetime (De Win et al. 2005). It may be argued that research like this is studying a reckless personality type rather than the long-term neurocognitive effects of a drug.

Many studies have found that MDMA does affect 5-HT metabolism and decreases 5-HIAA concentrations in cerebral spinal fluid (Stanley, Traskman-Bendz, and Dorovini-Zis 1985; Wode-Helgodt and Sedvall 1978). However, some studies have failed to link these findings to behavioral or long-lasting psychological changes from MDMA use. One study employed moderate users (22–50 lifetime exposures) and heavy users (60–240) of ecstasy with minimal lifetime exposure to other drugs. Few differences were found between ecstasy users and non-users on a battery of neuropsychological tests. However, heavy users did show some differences on measures of impulsivity and mental processing (Halpern et al. 2004). These findings suggest that there may be other factors, such as impulsivity or poly-drug use, that contribute to the neurocognitive deficits found among ecstasy users in studies that do not control for poly-drug use.

Some retrospective studies have been unable to find neurocognitive deficits in ecstasy users. Back-Madruga et al. (2003) recruited 22 recreational ecstasy users and compared them to 28 controls on a comprehensive battery of neuropsychological tests and found no significant differences. However, they did find that ecstasy users who reported heavy use had lower scores on non-verbal memory. It should be noted that this might be more closely correlated to a drug-seeking and impulsive personality type rather than the drug itself. It may be intuitive to think that MDMA's toxic effects on the brain should be studied in animal models, but even some of these studies have inherent limitations.

Many animal studies do show serotonergic neurotoxicity after administering MDMA to rats. However, some of these studies may have limited external validity due to methodological issues. For instance, doses of the drug used in animal studies are often much higher compared to what humans would typically consume. Also, the drug is typically administered more frequently (leaving little time to recover) and intravenously, which is virtually unheard of in humans. For instance, Commins et al. (1987) administered 10, 20, or 40 mg/kg (compared to the typical 1.5 mg/kg in humans) twice a day for four days (which is only representative of severe drug abuse or binging), and found damaged axon terminals in the striatum and somatosensory cortex

in rats. In addition, it has been found that there are large differences in MDMA metabolism and in the formation of neurotoxic metabolites between rats, non-human primates, and humans (De La Torre and Farré 2004).

Although MDMA has been widely studied, there is still debate on its level of neurotoxicity and its implicated dangers. However, the FDA has deemed it safe enough for clinical research to be conducted in the treatment of PTSD. Importantly, none of the clinical trials employing rigorous experimental controls have found long-term neurocognitive deficits in their participants.

PSYCHOPHARMACOLOGY OF MDMA

MDMA is a ring-substituted methamphetamine typically used in the hydrochloride salt form, which is an off-white colored powder (Shulgin 1986). The drug has structural similarities to both amphetamine and the psychedelic mescaline. MDMA has traditionally been considered a psychedelic amphetamine; however, it has been contended that the drug may belong to a unique class of drugs called "entactogens" (Nichols and Oberlender 1990). The drug's primary mechanism of action is on the 5-HT transporter, which results in excessive serotonin in the synaptic cleft but also interacts with other neurotransmitter systems, including dopamine and norepinephrine (Green, Cross, and Goodwin 1995). MDMA also acts to increase the release of oxytocin and vasopressin, which has been found to produce acute pro-social behaviors in rats (Ramos et al. 2013). These specific mechanisms will be discussed in more detail, but first the psychological effects of MDMA will be noted.

Liester et al. (1992) interviewed 20 psychiatrists to explore the phenomenological qualities of their personal experiences with MDMA. They found that the positive drug effects included sensory intensification, increased awareness of emotions, changes in interpersonal relationships, and slight ego dissolution. The psychiatrists reported that the negative effects of the drug included temporary anorexia, trismus (jaw tension), bruxism (teeth grinding), and motor restlessness. Many of the psychiatrists reported that their MDMA use resulted in long-lasting improvements in their attitudes and behavior and the drug has a potential as a therapeutic catalyst. Another study found that when MDMA was given to participants (1.5 mg/kg p.o.), the subjective effects included euphoria, a sense of well-being, moderate de-realization, and heightened sensory awareness (Liechti et al. 2000a). These effects are primarily mediated by the increased concentration of 5-HT in the synaptic cleft, which was originally discovered in preclinical animal models.

Animal studies have shown that serotonin reuptake inhibitors (SSRIs) block the effects of MDMA. Gudelsky and Nash (1996) found that MDMA produces increased concentrations of extracellular 5-HT in the striatum and prefrontal cortex in rats but is attenuated with the administration of fluoxetine. SSRIs also inhibit the 5-HT-induced behavioral effects of MDMA (Callaway, Wing, and Geyer 1990), and protect against 5-HT-induced neurotoxicity (Schmidt 1987). These findings show the strong action of MDMA on the 5-HT transporter. However, only human studies can reveal the receptors involved in the more nuanced psychological effects of the drug.

Matthias Lietchi and Franz Vollenweider have conducted a series of double-blind placebo-controlled studies to determine the receptors responsible for the specific psychological effects of acute MDMA administration using pretreatments of three different receptor ligands. In one of these studies, the researchers used haloperidol (1.4 mg, i.v.), a D_2 antagonist, as a pretreatment to orally administered MDMA (1.5 mg/kg, p.o.). They found that haloperidol attenuated the euphoric and mania-like effects of MDMA but had no effect on other subjective effects (Liechti and Vollenweider 2000a). These findings show that MDMA's action on the D_2 receptor is responsible for the amphetamine-like effects of the drug. Another of these studies used the drug citalopram (SSRI that acts on the 5-HT transporter). When participants were pretreated with citalopram intravenously (40 mg), prior to orally administered MDMA (1.5 mg/kg), most of the psychological and physiological effects of MDMA were attenuated (Liechti and Vollenweider 2000a). In other words, the 5-HT transporter modulates the acute effects of MDMA, which include reduced anxiety, acute anti-depression, and increased insight, as well as slightly increased heart rate and blood pressure. Ketanserin, a $5\text{-HT}_{2A/C}$ antagonist, was also used to determine how MDMA interacted with these receptors. When participants were pretreated with Ketanserin (50 mg p.o.) and 1.5 mg/kg MDMA, there were statistically significant reductions in sensory and perceptual amplification, but these didn't attenuate other aspects of the drug effect (Liechti et al. 2000b). Interestingly, part of the drug effect is dependent on the influx of the neuropeptide oxytocin.

One of the hallmark effects of MDMA use is the feeling of closeness and affiliation. It has been established in both animal studies and human studies that this is the result of an increased release of oxytocin. Thompson et al. (2007) found that when Winstar rats are injected with MDMA (5 mg/kg, i.p.), they spend more time laying closer together. After the rats were perfused, Fos immunochemistry revealed that oxytocin-containing neurons were activated in the supraoptic and paraventricular nuclei of the hypothalamus. In humans, it has been found that MDMA significantly increases blood plasma levels of oxytocin, and the subjective pro-social feelings are positively correlated to the oxytocin levels in the blood (Dumont et al. 2009). The increased sociability and feelings of closeness with others may also be due to the brain regions activated during the use of the drug.

Bedi et al. (2009) conducted an fMRI study that investigated the neural activation after participants were given MDMA and responded to angry, happy, and neutral faces. Participants that received MDMA (1.5 mg/kg, p.o.) reported feelings of increased sociability and had attenuated left amygdala activation in response to angry faces. Also, they found that there was increased activation in the ventral striatum in response to happy faces. This shows that the rewarding subjective effects (and possibly the therapeutic effects) of the drug may be due to reduced awareness of negative social cues and the enhancement of positive social cues.

Another fMRI study, of specific importance to the clinical use in posttraumatic stress disorder, investigated neural responses while processing autobiographical memories (Carhart-Harris et al. 2014). Participants ingested 100 mg MDMA (or placebo) and read their own favorite and worst memories while inside an fMRI. The participants that consumed MDMA reported that their worst memories were less negative while their favorite memories were more positive than those of the placebo group. The brain regions that were attenuated while reading their worst memories included the left anterior cingulate cortex, left amygdala, and temporal cortex. In addition, the executive regions of the hippocampus were activated while processing their worst memories. This is important because it may highlight some mechanisms that make MDMA an effective drug in treating posttraumatic stress disorder.

The results of Carhart-Harris et al. (2014) show that there is decreased amygdala activation and increased anterior cingulate cortex activation when participants who have ingested MDMA respond to their worst memories. This presents a mirror image of the neural activation shown by people with posttraumatic stress disorder when faced with fear. For instance, imaging studies show that when people with posttraumatic stress disorder undergo a conditioned fear paradigm, the left amygdala is *strongly* activated while the anterior cingulate cortex is *deactivated* (Bremner et al. 2005). MDMA, by affecting the left amygdala, the anterior cingulate cortex, and the executive areas of the hippocampus, may facilitate memory reconsolidation. These studies were published while the safety and efficacy of MDMA in treating posttraumatic stress disorder was being investigated by Michael Mithoefer in the United States and Peter Oehen in Switzerland.

TREATING POSTTRAUMATIC STRESS DISORDER WITH MDMA

In order to fully understand the possible mechanisms that underlie MDMA's effectiveness in treating posttraumatic stress, a rudimentary explanation of the disorder and the complications in treating it must first be reviewed.

The DSM-IV defines PTSD as a stress and anxiety disorder which follows a traumatic event. Three symptom clusters characterize the disorder: re-experiencing symptoms, avoidance symptoms, and hyper-arousal symptoms. These symptoms are often chronic and hard to treat. The Veteran Affairs estimates that only 9.5% of veterans diagnosed with PTSD are actually receiving treatment (Seal et al. 2010). This may be due to the marginal efficacy of current pharmacotherapy and psychotherapeutic options. Currently, only two pharmaceuticals are approved for treating PTSD: sertraline and paroxetine (Pollack et al. 2001).

Many psychotherapeutic options are available, but some have high dropout rates. Prolonged exposure therapy (PE) is thought to be the first-line treatment for PTSD, but one study found that only 6.3% of veterans being treated with psychotherapy are actually receiving trauma-centered therapy (Shiner et al. 2013). This is likely due to the emotionally demanding nature of exposure therapy, which causes the dropout rates to hover around 30% (Cloitre 2009). Although Cognitive Processing Therapy (CPT) has fewer completed clinical trials than PE, the treatment has a lower dropout rate and a promising treatment response. Monson et al. (2006) found that 40% of patients receiving CPT no longer met criteria for PTSD, while only 16.6% of patients dropped out of treatment prematurely. An emerging and somewhat controversial treatment for PTSD is Eye Movement Desensitization Reprocessing (EMDR) therapy, which shows comparable effects to behavioral therapies (Bradley et al. 2014; Davidson et al. 2001; Van Etten et al. 1998). Even with the emerging therapies, PTSD remains a chronic disorder and is difficult to treat.

First, trauma often affects the patient's ability to form trusting interpersonal relationships, which can affect the "working alliance" between the patient and therapist (Doukas et al. 2014). Another factor causing high dropout rates in therapy is that many people with PTSD have a small window of "optimal arousal" or "therapeutic threshold" (Foa et al. 1986). The reemerging thoughts brought up in therapy often cause distress and sometimes dissociation in patients. MDMA, and its cumulative psychological effects, has been found to mitigate some of these difficulties in treating PTSD.

The efficacy of MDMA in treating PTSD may result from a sum of its acute positive psychological effects. Some clinicians have stated that in one MDMA-assisted psychotherapy session, the patient can have results equivalent to five months of weekly therapy (Riedlinger and Montagne 2001). The increased trust allows for the patient to feel more comfortable sharing his or her trauma with the therapist, while the increased insight, memory, and attention allow patients to remember more details of the trauma.

When traumatic memories emerge during the MDMA experience, they are often seen as less threatening and can result in memory reconsolidation (Doblin 2002). This idea is supported by the study that found that negative autobiographical memories are perceived as less negative under

the influence of MDMA (Carhart-Harris et al. 2014). Also, the trust between patient and therapist may allow for more material to be discussed. Grinspoon and Bakalar (1986) have stated that "many patients report how much more they trust the therapist and how much closer they feel to the therapist after one such session." If, as many believe (Moras and Strupp 1982; Gomes-Schwartz 1978), the strength of the therapeutic alliance is the best predictor of a good outcome in therapy, this characteristic of MDMA would be of very general usefulness. The increased trust and prosocial effects, which help form the therapeutic alliance, are a result of the modulation of oxytocin. Both of these factors—the increased trust and decreased anxiety associated with the trauma—are the proposed mechanisms of therapeutic efficacy.

It is important to note that MDMA is thought to be a therapeutic catalyst rather than a "cure" for PTSD. Non-drug psychotherapy sessions are conducted before and after the MDMA-assisted psychotherapy. The initial non-drug sessions are to prepare the patient for the MDMA experience, while the follow-up sessions are used to solidify any insights gained or alleviate any difficulties experienced during the drug therapy sessions (Mithoefer et al. 2011).

CLINICAL TRIALS OF MDMA-ASSISTED PSYCHOTHERAPY

In 2010, the first clinical trial of MDMA-assisted psychotherapy for PTSD was concluded after 19 years of banned research. Mithoefer et al. (2011) conducted a randomized, placebo-controlled, double-blind, and crossover design study consisting of 20 participants showing a large effect size (Cohen's $d = 1.24$). All the participants in the study had chronic, treatment-resistant PTSD.

In this study, the participants were given a 125-milligram capsule of MDMA in the morning prior to an eight-hour psychotherapy session. Interestingly, there were two therapists: a male psychiatrist and a female co-therapist. One practical reason for this is that, in case one therapist had to be relieved, there was always another present with the patient. Another reason is that often, depending on the type of trauma, the patient can relate to one sex better than the other. The therapy style used was a modified form of LSD-assisted psychotherapy developed by Stan Grof (Pahnke et al. 1971). After the eight-hour session, the patients stayed overnight at the facility to ensure that there weren't any complications after the drug effects wore off, as well as to ensure there was support available if it was needed.

The primary outcome measure was the Clinician Administered PTSD Scale (CAPS) and was given to the patients four days after the first and second drug sessions. After the first MDMA session, the treatment group had a 41.4 (SD = 8.4) point reduction on the CAPS compared to a 5.5 (SD = 10.3) point reduction in the placebo group. After the second MDMA session, the CAPS scores in the treatment group decreased another 8.5 (SD = 6.5) points compared to 7.3 (SD = 8.0) points for the placebo group. At the two-month follow-up, the researchers found an 83.3% clinical response (defined as >30 point reduction in CAPS) in the treatment group. At this point, the placebo group was offered two open-label MDMA-assisted psychotherapy sessions. Seven of the eight members in the placebo group volunteered for two MDMA-assisted psychotherapy sessions. This group showed a 100% clinical response. In total, 16 of the 20 participants no longer met criteria for PTSD at the two-month follow-up.

The researchers also conducted a long-term follow-up on the participants 17 to 74 months (mean = 45.4; SD = 17.3) after exiting the study (Mithoefer et al. 2012). They found that the clinical improvements were sustainable over time and there were no statistically significant changes in the CAPS score. All of the participants except two still no longer met criteria for PTSD. The profound results from this study caused a surge in media attention, as well as prompting other researchers to start planning further investigations.

Oehen et al. (2012) conducted the second MDMA-assisted psychotherapy study, since the drug was banned by the DEA. This study recruited 12 treatment-resistant participants with PTSD. The design of the study was similar to that of Mithoefer et al. (2011). One difference is that there was an active placebo group, which received low-dose (25 mg) MDMA, while the treatment group received 125 mg MDMA.

This study reported a 23.5% reduction in CAPS scores in the full-dose group but did not show statistically significant results ($p = 0.066$). However, it has been argued that the statistical analysis used by the researchers was not appropriate because of the small sample size (Chabrol 2013). Henri Chabrol contended that the effect size provides a more realistic picture of the results, which produced a large effect (Cohen's $d = 1.08$).

Both studies completed thus far have shown impressive results. However, the efficacy of MDMA-assisted psychotherapy needs further investigation. The two successful Phase 2 clinical trials have shown that MDMA-assisted psychotherapy is safe and effective, which will allow for larger sample sizes in future Phase 3 trials.

DISCUSSION

The psychopharmacology of MDMA has been extensively studied over the past 20 years. However, attempts by scientists and the government to show the neurotoxic effects in humans have only produced equivocal results. For many years, MDMA research had been biased towards showing the neurotoxic effects of the drug while ignoring the clinical applications. The shifts in policies are reassuring and could not have come at a more critical time.

The prevalence rate for PTSD in the general population is 7.8% and 13.8% amongst veterans (Kessler et al. 1995). However, these figures may be largely underestimated due to many veterans unaccounted for or not reporting symptoms due to stigmatization. The economic burden of PTSD and other anxiety disorders is estimated to cost 43.2 billion dollars annually (Greenberg et al. 1999). More importantly, a recent report from the Veteran Affairs claims that an average of 22 veterans are dying by suicide each day (Carney 2014). This statistic acknowledges some serious shortcomings in the treatment options available for PTSD. Clearly, new therapeutic developments are needed. The current pharmacotherapies available, which are generally SSRIs, are only effective in treating 20 to 30% of patients with PTSD (Stein, Ipser, and McAnda 2009). Psychotherapeutic options are effective but intolerable by some patients due to the emotionally taxing nature of exposure therapies. Specifically, PE is one of the most intolerable psychotherapeutic options and is only practiced by a small minority of Veteran Affairs clinicians (Shiner et al. 2013). Other options, such as CPT and EMDR, are emerging but have not been as extensively studied as PE.

The nature of PTSD (avoidance, hyper-arousal, and re-experiencing symptoms) makes therapy inherently difficult for patients. Patients suffer from emotional numbing due to avoidance patterns or become hyper-aroused (anxious) due to re-experiencing their traumas. MDMA, resulting from its acute positive psychological effects, may be able to break this debilitating cycle. Patients find that the reduced anxiety caused by MDMA allows them to investigate their traumas without becoming hyper-aroused. Also, the feelings of trust, which are mediated by oxytocin release, allow for the patient to feel more comfortable in sharing intimate details of his or her trauma. One other contributing factor may be the amphetamine-like effects of the drug. Talk therapy, especially when oriented around trauma, can be exhausting, which causes patients to become hypo-aroused or disinterested. The amphetamine-like effects allow the patient to remain engaged during longer therapy sessions.

Preliminary results from the two completed MDMA-assisted psychotherapy clinical trials show promising results. More research is needed to solidify these findings and to further develop the treatment. The economic and social costs of PTSD demand that innovative and promising treatments become available to the many suffering from PTSD.

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