Article

The Psychiatric Utility of MDMA

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Objective: This paper aims to compile the history, available data, pharmacology, and notable studies of 3,4-Methylenedioxymethamphetamine (MDMA), more commonly referred to as ecstasy, order to assess any potential medical utility.
Methods: Literature Review
Discussion: MDMA, when combined with appropriate psychotherapy, appears to have a statistically significant and rather large effect on the reduction of PTSD symptoms. It has also been investigated for use in alcohol use disorder, autism spectrum disorder, and social anxiety disorder. Phase III clinical trials are underway, and MDMA assisted psychotherapy could be and FDA approved treatment for PTSD as early as 2021. Caution must be used to ensure there are no significant risks including addiction or long-term side effects from use, but early clinical trials suggest a reasonable safety profile.

Introduction

Generally referred to as "ecstasy," 3,4-methylenedioxymethamphetamine (MDMA) has been a popular drug used for recreational purposes since the 1960s and has been investigated for potential psychiatric utility in the treatment of several disorders. Other street names include Adam, "molly," XTC, E, X, MDM, and EA-1475. MDMA is a highly polarizing agent within the general public and medical community and has an extensive list of potential benefits and adverse effects. It has garnered attention for its potential use in helping patients suffering from symptoms of PTSD and other psychiatric disorders.

History

German chemist Anton Kolisch first synthesized MDMA for the pharmaceutical company, Merck, in 1912 [8,9]. Much like the discovery of lysergic acid diethylamide (LSD) in 1943, MDMA was discovered accidentally during efforts to synthesize a new hemostatic agent [7]. MDMA was initially classified as an intermediate compound in the process of synthesizing methylhydrastinine, and Merck had no apparent interest in the compound at that time [5,8]. There was no record or mention of MDMA by the company until 1927 when another chemist studying adrenaline and ephedrine noted the structural similarity of MDMA to these compounds. Some initial studies were undertaken, which concluded that the compound did not have 'pure sympathetic effects.' The next records of MDMA from Merck were not until 1952 [8]. The predominant research at that time appears to have been looking into the toxicology of the compound. In the 1950s, the United States Army at the University of Michigan began studying MDMA for toxicology purposes. There is no evidence of human testing of MDMA until at least 1960 [8,9].

By the 1960s, while little was known about MDMA, word had gotten out about the desirable effects. In 1970, before any legitimate human studies, law enforcement seized MDMA tablets from the streets of Chicago [8,11]. American chemist Alexander Shulgin was next to advance the knowledge of MDMA. Well known for his interest in psychoactive compounds and prior to his work with MDMA, Shulgin had focused on the similar compounds 3,4-Methylenedioxyamphetamine (MDA) and 3-methoxy-4,5-methylenedioxyamphetamine; 5-methoxy-MDA (MMDA). While working at San Francisco State University in the 1970s, various colleagues had spoken to him about the effects of the drug, attracting his interest. In 1978, Shulgin, along with medicinal chemist David Nichols published a paper discussing the effects of MDMA in humans.

In this paper, the psychotomimetic properties of the drug were described as follows: "Qualitatively, the drug appears to evoke an easily controlled altered state of consciousness with emotional and sensual overtones. It can be compared in its effect to marijuana, to psilocybin devoid of the hallucinatory component, or to low levels of MDA [12]." At the time, MDA was a structurally similar, better known, schedule 1 drug that produced euphoric and stimulating effects, but was never as popular as MDMA. In 1986 and 1990, Shulgin published two more papers discussing MDMA and even suggesting that it may have utility as an adjunct to psychotherapy due to its observed effects of disinhibiting the patient [9,10].

In addition, to his research contributions, Alexander Shulgin is thought to have introduced MDMA to Leo Zeff in 1977 [9]. Dr. Zeff was an American psychologist and psychotherapist who had been using LSD in his practice since 1961 and gained notoriety for famously nick naming MDMA "Adam" as he thought that it returned the user to a "primordial state of innocence [9]." There is limited data discussing the specific psychotherapeutic techniques that Dr. Zeff employed, but he is well known as an early advocate for the use of MDMA and encouraged its use amongst his colleagues [9,10].

MDMA was introduced as a street drug at some point in the 1960s [5,8]. Most of the production was thought to have been from underground chemists, and the purity was inconsistent. MDMA was initially thought of as a legal alternative to MDA, which had been scheduled as a controlled substance in 1970. The drug initially surfaced in the Midwest, and until 1974 nearly all street samples of the drug were confiscated with the first recorded seizure in Chicago in 1970. MDMA was first detected in Canada in 1974 and was quickly scheduled as a controlled substance in 1976 [5]. From 1975-1980 the use of MDMA became more localized to the West Coast with street samples being found in multiple other states [8,11].

In the 1980s, psychotherapists using MDMA attempted to keep the drug in the clinical research community to avoid the repercussions that would follow if the drug were to become diffusely popular. However, by this time, MDMA had been used on the streets for years, and in the early 1980s, MDMA was rebranded as "Ecstasy [3,8,9]." Its use became popular, especially at parties or "raves." In 1984 the DEA finally moved to ban the compound due to rising seizures of the drug by police and concerns over increasing use nationwide. Despite the clinical MDMA research community's attempt to stop the drug from being banned, in 1985, MDMA was placed in emergency Schedule One classification, and from that point forward, its status as a scheduled drug has become permanent. As expected, since 1985, research into MDMA became profoundly difficult. Compared to Europe, the use of MDMA in the USA in the 1980s was relatively limited; in Europe, it was a popular recreational drug during this time. Recreational use of MDMA began to rise significantly in the mid-1990s in the USA [11].

Pharmacology

MDMA is structurally similar to amphetamines and certain hallucinogens such as mescaline [5]. Despite its relatively simple chemical structure, MDMA manages to have a vast range of effects on receptors, neurotransmitters, and hormone release. MDMA's most notable effects are on monoamines such as serotonin, dopamine, and norepinephrine through multiple mechanisms; the main effect of acute MDMA exposure is increased extracellular serotonin concentration. MDMA is known to inhibit serotonin transporter (SERT), dopamine transporter (DAT) and norepinephrine trans-

porter (NET), which leads to impaired reuptake and increased extracellular levels of the monoamines [5,13]. This is thought to be due to competitive inhibition, as MDMA acts as a substrate for these transporters. MDMA is a more potent inhibitor of SERT than DAT or NET leading to a comparatively greater increase in the concentration of extracellular serotonin Once inside, a monoamine neuron MDMA binds to and inhibits vesicular monoamine transporters (VMAT) and, more specifically, vesicular monoamine transporter 2 (VMAT2). The purpose of VMAT2 is generally to transport monoamines from cellular cytosol into synaptic vessels. This inhibition results in an increased concentration of dopamine, serotonin, and norepinephrine in the cellular cytosol [5,13,14]. MDMA then leads to direct release of serotonin, dopamine, and norepinephrine into the extracellular space by reversing the direction of the flow of the monoamines through their native transporters at the cellular membrane once intracellular concentrations of the monoamines rise to a significant enough level to create a concentration gradient [26]. The releasing effects of this method are increased in serotonin and norepinephrine compared to dopamine [5].

MDMA is also known to bind directly to several important neuroreceptors, although for the most part, it binds to them weakly suggesting its activity at VMAT2 and the monoamine transporter inhibition is more important [5,13]. These receptors include H1 histaminergic, B-adrenergic, serotonergic, dopaminergic, and muscarinic receptors. The most robust serotonergic activity on a receptor is on the 5-HT2B receptor as an agonist, although this currently has unclear significance. MDMA is also active at the trace-amine associated receptor (TAAR1), where it acts as an agonist. TAAR1 has many functions, including regulating neurotransmission in dopamine, serotonin, and norepinephrine neurons in the central nervous system. Activation of TAAR1 by MDMA leads to protein kinase A and protein kinase C activity, which leads to the phosphorylation of the monoamine transporters DAT, SERT, NET in the neuron [5,13]. This leads to either reversal in the direction of transport systems, moving cytosol neurotransmitters to the synaptic cleft, or withdrawal of transporters back into the cell functionally leading to inhibition. These actions increase the extracellular concentrations of serotonin, dopamine and norepinephrine. It has also been shown that MDMA binds to the sigma-1 and sigma-2 receptors. The exact role of these receptors is unknown, but other psychoactive drugs bind to it, including phencyclidine (PCP), methamphetamine, and dextromethorphan, among others [5]. The sigma-1 receptor has gotten some interest as being a potential target for antidepressant and anxiolytic medication as some current psychiatric medications act as agonists at the receptor, including citalopram and fluvoxamine [5,14].

MDMA is known to have hormonal effects leading to increases in the plasma concentrations of cortisol, prolactin, dehydroepiandrosterone (DHEA), vasopressin, and oxytocin [5]. Oxytocin is of specific interest due to the role it is thought to have in prosocial feelings. In a study by Dumont et al. published in 2009, they showed that increases in oxytocin in blood levels correlated more closely than concentrations of MDMA in the context of increasing prosocial behavior [15]. Other studies have not demonstrated this relationship but have confirmed an increase in oxytocin. The behavioral effects of this hormone on the user of the substance are still unclear.

PTSD Research

Psychedelics have been explored as potential adjuncts to psychotherapy since the early 1900s, including psilocybin, LSD, and MDMA [3,7]. MDMA has garnered particular attention as an agent to help treat post-

traumatic stress disorder (PTSD) due to the potential to temporarily decrease the fear response during a therapy session while increasing trust and empathy in the therapeutic relationship [1,2,4]. In the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), a diagnosis of PTSD requires exposure to an actual or threatened death, serious injury or sexual violence which could be experienced in several different ways including directly experiencing or witnessing a traumatic event, learning about a close friend or family member's traumatic experience or repeated or extreme exposure to aversive details of a traumatic event. The core symptoms of PTSD include intrusive symptoms such as nightmares or flashbacks related to the incident, avoidant behavior, negative mood, and alterations in arousal leading to hypervigilance, sleep disturbance, concentration deficit, or increased startle response [2,17]. It is difficult to estimate the prevalence of PTSD, but the World Health Organization World Mental Health (WMH) Survey analysis examining data from 26 different countries, and a total of 71,083 respondents estimated the lifetime prevalence of PTSD to be about 3.9% globally. These surveys were completed between 2001-2012 [16]. PTSD takes a significant toll on the well-being of individuals along with a large but difficult to estimate economic cost through lost productivity and treatment.

Current guidelines in the treatment of PTSD recommend the use of psychotherapy as first-line treatment over current pharmacological options. The specific therapies used are exposure therapy and trauma focused cognitive behavioral therapy (TF-CBT). There are only two medications that are FDA approved to treat PTSD currently: sertraline and paroxetine. In clinical practice, more medications are used to treat PTSD, including other selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antipsychotics, benzodiazepines, and many other medications [17]. Therapy is always recommended, but not always available and not everyone will respond to treatment with medication or therapy.

Due to the scheduling of MDMA in 1985 there were no clinical trials of the substance until the year 2000. In 1986 the Multidisciplinary Association for Psychedelic Studies (MAPS) filed a Drug Master File application and then in 2001 an Investigational New Drug (IND) application. This allowed the MAPS to work within FDA guidelines to study the safety and efficacy of MDMA as an adjunct to psychotherapy for PTSD [19]. MDMA is thought to be an excellent drug to use in concert with psychotherapy due to positive effects on trust and empathy, along with the limited perceptual disturbance and generally retained cognitive function [2]. Six MAPS-sponsored randomized, double-blind phase two studies will be discussed, that took place between 2004-2017, although there have been general tolerability and case studies that showed promise as well [25]. In 2017, after reviewing the data in 2016, the FDA granted a Breakthrough Therapy Designation to MDMA and approved two phase III trials, which started in 2018 but do not yet have published results [19].

The first randomized controlled pilot study was done by Mithoefer et al. with enrollment from 2004-2008 and follow up being completed in 2008 [18]. Candidates for the study were required to have Chronic PTSD with symptoms lasting over six months, along with the Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV) scores ≥ 50. This was also true of the other 5 MAPS sponsored phase II studies except for one study requiring a score of ≥ 60 in Canada [18,19]. Subjects included men and women, both civilians and veterans, and they

must have been at least age 18 years old. It was required that they had failed one previous pharmacotherapy or psychotherapy to treat PTSD which they counted as an inadequate response to previous treatment; the average amount of medications failed for this initial study was 4.2 psychiatric medications with at least one unsuccessful course of psychotherapy in 75% of the patients in the study. Participants were not excluded for meeting criteria for anxiety or depressive disorders but were excluded if they met the criteria for a psychotic disorder, bipolar disorder, eating disorders, or borderline personality disorder. The other exclusion criteria included significant medical diagnoses that could be exacerbated by MDMA, pregnancy, or weight under 48 kilograms. Those with substance use disorders were excluded if the diagnosis was active within 60 days of screening [18,19].

In this first study done by Mithoefer et al. of the group of six phase II clinical trials coordinated by MAPS, 20 patients underwent the study after two patients ended up dropping out due to relapse of depression and inability to travel for the study. The subjects were randomized into two groups in a double-blind fashion to receive two experimental psychotherapy sessions with MDMA administration (12 patients) or with placebo (8 patients). Patients were required to taper off of all psychotropic medications prior to the study, and the only psychotropic medications used in concert with the MDMA or placebo were as needed zolpidem or lorazepam generally for insomnia treatment [18].

No greater than six weeks before the first experimental sessions, each subject underwent two 90 minute introductory sessions helping them become familiar with the experimental protocol. A male and female co-therapist team of a psychiatrist and psychiatric nurse were present for all therapy sessions in the study, and the same team was used each time for a given patient. They had been trained in MAPS Therapy Training Program based on the method described in the MDMA-assisted Psychotherapy Treatment Manual, so there was consistency between sessions. In addition to the experimental sessions, there were non-drug therapy sessions for both the treatment and control groups. In total, outside of the introductory sessions, there were two experimental sessions, where administration of drug or placebo occurred, along with a standard eight integration sessions focusing on experimental sessions and additional emotional processing. There was some variation in time elapsed between sessions, but all non-drug psychotherapy sessions occurred 1-7 days apart and 3-7 days after the experimental sessions [18,19].

Experimental sessions took place in a comfortable, aesthetically pleasing environment with a sofa capable of reclining, with the co-therapists sitting on both sides of the patient in chairs. In this first study with Mithoefer et al., the dosage of MDMA was selected to be 125mg, and the placebo was simply lactose. MDMA or placebo was given at 10 am, and the sessions lasted 8-10 hours with a required overnight stay the night of the experimental session. The subject would either have their eyes closed or would wear eyeshades as music played. This music was designed to be initially relaxing and then transition to emotionally evocative; the music was identical for each subject, but they did have the power to skip over songs and replace them with silence instead. The co-therapists would help guide patients through the experience with a therapeutic conversation and the encouragement of introspection, the proportions of each was based on the patient response and clinical judgment of the therapists. An optional supplemental dose of 62.5mg of MDMA was offered 2-2.5 hours after administering the initial dose if deemed safe and appropriate, which was accepted in

22 of the 23 sessions in which it was an option. There was also a cross-over section of the study, which was open-label, and thus the data is excluded in the final results; however, it is essential to note this arm of the study for long-term follow-up purposes. This cross-over arm of the study only included those in the placebo group who were not exposed to MDMA and was not offered until after the two-month follow-up data was acquired, which was the endpoint of the initial study. Functionally, it means that 19/20 of the subjects eventually ended up being exposed to MDMA [18].

The onset of effects in those patients treated with MDMA was generally between 45-75 minutes after ingestion [18,19]. Peak effects occurred 2-2.5 hours after the initial dose and lasted between 4-5 hours and 5-6 hours in those that received the supplemental dose after 2-2.5 hours as above. This study demonstrated statistically significant increases in blood pressure, heart rate, and temperature when comparing pre-session to highest recorded during session values. However, there was no significant difference between the groups in vital sign measurement at the completion of the session measured at 6 hours after ingestion. Side effects reported by patients were more common in the MDMA group versus the placebo group, included nausea, dizziness, loss of appetite, impaired balance, feeling cold, and jaw tightness. On the treatment day, the placebo group had higher rates of anxiety and insomnia with comparable rates of headaches and fatigue. The most striking of these effects were jaw tightness with 79% of those in the MDMA group experiencing it versus only 19% of placebo; nausea with 50% in the MDMA group versus 13% in placebo, and impaired balance with 25% experiencing it in the MDMA group versus 0% in the placebo group. They also discussed side effects experienced at some point in the seven days after the treatment with generally similar rates of side effects except for an increase in irritability and loss of appetite in the MDMA group and insomnia in the placebo group. Side effects generally resolved on their own, but some patients were given sedative-hypnotics or non-steroidal anti-inflammatory drugs following experimental sessions [18].

The primary outcome of the study was the reduction in CAPS-IV scores. Patients' scores were compared from less than four weeks before the first treatment with placebo versus MDMA (79.6 vs 79.2; p-value of 0.966), 3-5 days after the initial treatment (74.1 vs. 37.8; p-value of 0.013), 3-5 days after the second treatment (66.8 vs. 29.3, p-value of 0.002) and two months after the second treatment (59.1 vs. 25.5, p-value of 0.013). The PTSD symptoms, as measured by CAPS-IV, improved over time in both groups but the MDMA group showed a significantly greater improvement in symptoms compared to placebo as can be seen above. In order to correct for multiplicity, Mithoefer et al. examined mean differences between 'group × time' using independent *t*-tests with Holm's sequential Bonferroni correction (α). The reductions in CAPS-IV scores were found to be significant in all groups except the initial group prior to initiation of treatment as above. PTSD symptoms measure by Impact of Event Scale-Revised (IES-R), another PTSD rating scale but not the primary outcome of the study, followed a similar pattern of comparable improvement in symptoms. Clinical response was defined as >30% reduction from baseline in CAPS total severity score with 83.3% (10/12) in the MDMA group versus 25% (2/8) in the placebo group showing this improvement. Of note, there was no significant difference in scores between patients who received the supplemental dose versus those who did not. In order to try to evaluate for potential cognitive function change a battery of tests were performed prior to the first dosing of

MDMA and two months after the second dosing including the repeatable battery for the assessment of neuropsychological status (RBANS), Paced Auditory Serial Addition Test (PASAT) Trial 1 and 2, and the Rey-Osterrieth Figure 30-minute delay. At baseline, there were no significant differences between the MDMA or placebo receiving groups. Comparing the two groups at the two month follow up there again were no differences in any of the significant index scores [18].

After the completion of this study Mithoefer et al. attempted to investigate the durability of improvement in PTSD symptoms and published a follow-up paper in 2013 [20]. Due to the cross-over arm of the initial study, 19/20 of the initial patients ended up receiving MDMA. Due to a protocol amendment from the first study, eight subjects received three MDMA sessions, and 11 subjects received two MDMA sessions prior to long term follow up (LTFU) participation. All 19 of these initial subjects participated in the LTFU, with 16 of the 19 completing all outcome measures. The CAPS score was the primary outcome measure with the IES-R again being used along with a questionnaire designed to get information about various things including the perceived benefits or harms from the study. The LTFU questionnaire and questionnaire were mailed to the patients, and the CAPS was done over the phone or in-person by the same rater that had initially done the individual patient's CAPS. This investigation was conducted 17 to 74 months after completion of the final MDMA session with an average of 3.5 years per patient. At LTFU, 13% (2/19) of the patients had CAPS scores > 50, indicating relapse of PTSD with moderate to severe symptoms. When the three patients who did not complete the CAPS at LTFU are added, constituting intent-to-treat analysis, the number is 26% (5/19). The mean CAPS and IES-R scores at LTFU were not statistically different when compared to the two month mean scores indicating long term improvement in symptoms. While the questionnaire sent out was not a validated instrument, it did provide interesting information. No one felt that they were harmed by participation in the study. There was no change in substance abuse habits before versus after the initial study as patients had already informed the investigators of their substance use before the first study, the most common substance was recreational cannabis use with eight patients reporting intermittent use. Of note, one patient stated that he had again used MDMA prior to the completion of the LTFU in a semi-therapeutic setting to replicate the strategy used in the initial study. He had a friend be present during the study; however, he did not find this beneficial and reported no plans for further use of MDMA. All participants in the survey did state that they felt further sessions of MDMA, and psychotherapy would be helpful, either "at a later time point" or "soon after the first one." Overall, no lasting adverse medical or psychiatric effects were observed [20].

After the first study by Mithoefer et al., a group in New Zealand, Oehen et al. attempted to replicate the promising results from the initial study [21]. Patients were enrolled from 2006-2009 with follow up completed in 2011. The study inclusion criteria and design were essentially the same as those done by Mithoefer et al. with a significant difference in the control group. Instead of using an inactive placebo, low dose MDMA was used with 25mg given in the initial dose plus a possible 12.5mg supplemental dose. The full dose was again 125mg with a 62.5mg supplemental dose. This was done to try and address the difficulty with successfully double-blinding a powerful drug like MDMA to allow for the low dose group to experience detectable but likely sub-therapeutic effects. The sample

size was 12 with eight patients randomly assigned to the full-dose group and four to the lower dose group. There were three planned experimental sessions and CAPS scores were acquired at baseline prior to treatment, three weeks after MDMA session #2, 3 weeks after MDMA session #3 (the end of treatment), along with 2, 6 and 12 months after MDMA session #3.

Interestingly, in this study with the lower dose MDMA "active placebo" group, the CAPS scores increased slightly from baseline (63.5) versus three weeks after the study (66.5). Over the same period, the full-dose group's CAPS scores went from baseline (66.4) versus three weeks after the study (50.8) This constituted an average drop of 16.2 points or 23.5%. While this did show a decrease in CAPS score compared to the active placebo group, the difference was found to not be statistically significant with a p-value of 0.066. This study did show that the overall tolerability of MDMA was favorable in a clinical setting with no significant adverse events. It is unclear why this study did not show a statistically significant difference between the groups, but the authors suggested it could be related to cultural differences, the smaller sample size in general, or due to the higher overall CAPS scores at baseline of the Mithoefer et al. study [21].

As discussed above, this study by Mithoefer et al. was the first of six randomized, double-blind, controlled clinical trials at five study sites sponsored by MAPS. The studies all had similar designs allowing producing more consistent results. Some differences between the studies included the dosing of MDMA used in the treatment group and if they used a true placebo or active placebo as done by Oehen et al. Doses for the treatment group in these studies ranged from 75 mg, 100 mg, or 125 mg and placebo 0 mg, 25 mg, 30 mg, or 40 mg respectively. The data from the above Mithoefer et al. study is included in the final analysis of the MAPS trials [19,22]. Between the six studies, there were 105 patients: 31 in the control group and 74 in the active group. The baseline CAPS-IV scores were 85.8 for the treatment group and 81.3 for the control group indicating severe PTSD symptoms with slightly higher scores noted in the treatment group. Change in CAPS scores from baseline was significantly different between the groups with an estimated change in the active group of -30.4 and -10.5 in the placebo group with a p-value of < 0.0001. The percentage of patients no longer meeting criteria for PTSD after the second treatment for the active group was 54.2%, and for the control was 22.6%. The between-group effect size was large and calculated to be 0.8 using Cohen's *d*. A secondary outcome used in four of the six clinical trials was a reduction in The Beck Depression Inventory-II (BDI-II). The change in scores from baseline after the second treatment was -12.4 for the active group and -6.5 for the control; the difference between the groups did not quite meet statistical significance with a p-value of 0.053[19].

Throughout these clinical trials, there were four serious adverse events with three of them considered to be unrelated to treatment including suicidal ideation in a patient receiving active control in the context of a life stressor, suicidal behavior in a patient prior to the first treatment session, along with another patient developing appendicitis. The final serious adverse event was an exacerbation of pre-existing premature ventricular contraction in a patient after receiving 125mg of MDMA; the patient did recover without permanent issues but required overnight cardiac monitoring. During the treatment sessions, the most common adverse events experienced between the treatment and control groups were: anxiety (72% active vs. 48% control), jaw clenching (64% vs. 19%), dizziness (40% vs. 19%), nausea (40% vs. 19%) and loss of

appetite (49% vs. 23%). A transient elevation in vital signs was again noted, which resolved spontaneously after the experimental sessions [19].

As noted earlier, the results of these clinical trials were so encouraging that the MAPS group moved forward with phase III clinical trials, which are currently underway [19,22]. The reduction in PTSD symptoms when using MDMA assisted psychotherapy is impressive, especially when combined with the potential for long-lasting remission, as noted by Mithoefer et al. in their follow up study on average 3.5 years after completion of this treatment [20]. Overall, the use of MDMA when carefully monitored by medical professionals appears to be safe; however, further attention may need to be paid to patients with existing arrhythmias or other cardiac conditions. It is still unclear what the optimal dose of MDMA is as reasonable results were produced with doses of 75mg, 100mg, and 125mg; this will be investigated further in phase III clinical trials [19]. Due to the common use of MDMA recreationally, there are warranted concerns for drug abuse or misuse associated with using MDMA as a therapeutic treatment. At this point, MDMA, when combined with psychotherapy, appears to have a low potential for abuse. There were no adverse events related to MDMA seeking behavior or craving of the substance noted during the studies. In the follow-up study by Mithoefer et al., it was noted that one patient attempted to replicate the clinical trial conditions in their personal life and did use MDMA. This type of behavior will need to be monitored closely, going forward. A barrier to the widespread use of this method is the likely cost that will be associated with the psychotherapy and close monitoring of patients during and after administration of MDMA. While MDMA assisted psychotherapy will likely not become a first-line treatment for PTSD immediately, it does have clear potential to help certain patients who have failed other treatments. If the results of phase III clinical trials are equally positive, MDMA assisted psychotherapy could be an FDA approved treatment option for PTSD as early as 2021 [19,22].

Alcohol Use Disorder

While MDMA has not received as much attention as a possible treatment for certain addictions, compared to other psychedelic medications such as LSD or psilocybin, it has been postulated that it could be a potential treatment option for alcohol use disorder (AUD) [31]. The key features of AUD, according to DSM-V, include general life dysfunction related to alcohol use, difficulty cutting down on use, drinking more than intended, continued use in dangerous situations, and symptoms of tolerance and withdrawal. The economic and societal burden exerted by AUD is significant with a twelve-month and lifetime estimation of prevalence in the United States of 13.9% and 29.1%, respectively. Compared to the research on MDMA assisted psychotherapy for PTSD, there is a paucity of data investigating if this strategy could be effective for AUD [24].

To date, there is only one published study related to MDMA assisted psychotherapy as a treatment for AUD done by Sessa et al. It is an open-label safety and tolerability proof of concept study and is still ongoing, but they have presented preliminary data [23]. Subjects were adults with diagnosed AUD who had successfully undergone community alcohol detoxification. For the most part, the study design and exclusion criteria mimic what was used to investigate MDMA assisted psychotherapy for PTSD treatment. Subjects underwent an 8-week course of MDMA assisted psychotherapy with a total of 10 sessions utilizing motivational enhancement therapy. MDMA

was administered at sessions in weeks 3 and 6 at doses of 125mg with an optional 62.5mg booster dose 2 hours after. So far, Sessa et al. have released data about four patients who have completed this constituting a case series. They did not present data from a standardized rating scale such as the Alcohol Use Disorders Identification Test (AUDIT), but their primary outcome measured was drinking habits. The authors acknowledge that they are not reporting detailed outcome data concerning drinking patterns as the study is ongoing. Of the four patients followed for nine months after this treatment, two reported complete abstinence, and two reported single episodes of small amounts of alcohol use; none returned to daily or harmful drinking. No adverse events were noted during the study, and similar physiologic responses compared to similar studies were shown. The treatment appears to be well-tolerated, and the authors have discussed undertaking a future randomized placebo-controlled study [23].

Autism Spectrum Disorder and Social Anxiety

Autism spectrum disorder (ASD) is characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors. It is a neurodevelopmental disorder influenced by both genetic and environmental factors, but no clear unifying cause has been identified. The World Health Organization (WHO) estimates that the international prevalence of ASD is 0.76% while in the United States, a parent-reported survey averaged about 2.5% in 2014 [29]. In 2013 epidemiological data were collected from patients with ASD who were either MDMA experienced or MDMA naïve. After reviewing feedback from patients and formal assessment tools, it was hypothesized that MDMA could be helpful in the treatment of ASD who suffer from social anxiety disorder (SAD) [30]. SAD is generally characterized as intense fear or anxiety related to social situations leading to some degree of impaired ability to function. People with ASD are thought to be at greater risk of developing SAD [29].

Between 2014-2017 a randomized, placebo-controlled, double-blind study was undertaken to investigate if MDMA could have utility in treating SAD in patients with ASD [28]. A total of 12 participants were recruited and randomized to receive either placebo (four patients) or MDMA (eight patients) groups, and both received the same psychotherapy. To be eligible the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Axis I Research Version (SCID-I-RV) and Autism Diagnostic Observation Schedule (ADOS-2 Module 4) to confirm ASD diagnosis and a Leibowitz Social Anxiety Scale (LSAS) score of 60 or higher was required indicating diagnosis of SAD. Participants were at least 21 years of age and had never tried MDMA by self-report. The subjects were not required to have treatment-resistant SAD, but 8/12 (66.7%) had tried some sort of psychotropic medication in the past, and 10/12 (83.3%) had tried psychodynamic psychotherapy. The design and exclusion criteria were generally similar to the design used in the PTSD studies unless otherwise noted. There were three preparatory psychotherapy sessions before the experimental session, where patients were given MDMA or placebo. Three more sessions of integrative psychotherapy occurred over the following three weeks, followed by another experimental session one month after the first session. After three more psychotherapy sessions over three weeks, the study was completed [28].

During the preparatory psychotherapy sessions, the structure of the study was discussed with the patients, and rapport was established. Mindfulness therapy ad-

apted from dialectical behavioral therapy (DBT) was used in subsequent sessions to help support patients struggling with interpersonal relationships, emotional regulation, and distress tolerance. During the experimental sessions, patients were closely monitored and supervised similarly to the studies looking into PTSD. Four of the patients in the active group were to be given 75mg of MDMA in the first session and 100mg in the second, the other four were to be given 100mg of MDMA in the first session and 125mg in the second; however, for statistical analysis, all patients receiving MDMA were grouped together. The control was a true placebo in the form of lactose [28].

The primary outcome of the study was the mean change in LSAS scores from baseline comparing the active to the control group. An independent rater administered the LSAS at baseline, 1 day, 2 weeks, and 4 weeks after each experimental session and then again at six months after completion of the study; the same rater was used for the entire study. The study's primary endpoint was the change in LSAS score from baseline to 4 weeks after the second experimental session. Mean LSAS scores at baseline were 91.8 for the MDMA group and 83.3 for the control group, which improved to 46.4 for the MDMA group and 64.0 for the control group at four weeks after the second experimental session. The mean change in LSAS scores from baseline to the primary endpoint of -44.1 for the MDMA group and -19.1 for the control group constituted a significant difference in LSAS scores between the groups with a p-value of 0.036. The placebo-subtracted Cohen's *d* effect size was 1.1, which indicates a large effect size. At the six-month follow-up the change in LSAS scores from baseline remained essentially the same when compared to the change in scores from the primary endpoint with -47.7 for the MDMA group and -23.3 for the control group. Of note, one patient in the active group dropped out of the study for unclear reasons and is counted as a treatment failure. The rate of clinically significant changes in SAD symptoms from baseline was 6/8 (75%) with MDMA versus 2/4 (50%) with placebo with significant change defined as a change in LSAS score of 20 or more points [28].

No significant adverse events were reported in the study with the most common adverse events occurring in the experimental session in the MDMA versus placebo group being anxiety (75% in the MDMA vs. 25% placebo), difficulty concentrating (62.5% MDMA vs. 25% placebo), along with more frequent headache, fatigue, and sensitivity to cold in the MDMA group. A severe headache was reported. Other symptoms were similar between the groups, including 25% of patients experiencing suicidal ideation in both groups, but this was pre-existing in the medical history [28].

Although the sample size was small, the results were encouraging and warrant further investigation. Similar to the results from the PTSD studies, there is hope that treatment with MDMA and psychotherapy could lead to long term improvement in symptoms in patients with ASD who suffer from SAD.

Discussion

Recently, psychedelic compounds have been investigated as treatments several psychiatric disorders, with Ketamine already being an FDA approved treatment for treatment-resistant depression. LSD, psilocybin, and especially MDMA appear to have garnered plenty of excitement as well [17]. MDMA has primarily been investigated for use in patients with PTSD. MDMA or placebo was combined with standardized, trauma-focused therapy and administered in a controlled environment in these studies. MDMA, when combined with appropriate psychotherapy, appears to have a statistically significant and

rather large effect on the reduction of PTSD symptoms. These results have been so promising that phase III clinical trials are currently underway and if these are also positive MDMA assisted psychotherapy could be an FDA approved treatment option for PTSD as early as 2021 [19,22]. MDMA-assisted psychotherapy has also shown promising results for the treatment of alcohol use disorder, and autism spectrum disorder with social anxiety. As with all controlled substances, the risk for addiction needs to continue to be investigated, but thus far, the risk appears to be minimal when used in a controlled environment by medical professionals. There is also a lack of long-term data about the potential adverse effects of using MDMA, but it appears to be surprisingly well tolerated. Both addiction risk and long-term side effect risks will be studied more thoroughly during phase III clinical trials for PTSD. It is easy to be excited about the potential use of MDMA for treating PTSD and perhaps other psychiatric disorders. We must continue to review the research to make educated treatment recommendations for our patients going forward as more psychedelic treatments become available for clinical use.

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Sundahl, M. (2020, June). The Psychiatric Utility of MDMA. *The Journal of Psychedelic Psychiatry*, *2*(1).

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