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A Literature Review: The Efficacy of MDMA-Assisted PTSD Psychotherapy

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Abstract

Researchers have proposed that 3,4-methylenedioxymethampethamine (MDMA), an illicit psychedelic drug with widespread recreational use, may be a beneficial therapeutic adjunct in PTSD treatment due to its unique mood altering and prosocial effects. A growing body of clinical evidence points to MDMA-assisted psychotherapy as a promising alternative for individuals who have found current PTSD treatments unsuccessful. Within the past decade, several studies integrating MDMA administration with psychotherapy have seen clinical PTSD symptom reductions. Despite this, the therapeutic application of MDMA remains contentious. A range of in vitro experiments as well as studies in drug users and animal models have associated MDMA with adverse health consequences, including psychiatric distress, cognitive decline, and neurotoxicity. However, it remains a challenge to parse out whether these negative side effects are truly applicable in a clinical setting, where a chemically unadulterated and standardized dose is provided during a limited number of sessions. In this literature review, I will summarize the recent clinical trials on MDMA-assisted psychotherapy, point out the limitations of this research, examine potential adverse health effects, and outline important topics for future exploration.

Keywords — MDMA, post-traumatic stress disorder, drug-assisted therapy

1. Introduction

Post-traumatic stress disorder (PTSD) is a mental illness involving intrusive thoughts and flashbacks which can develop after an experience of severe trauma, such as armed conflict, natural disaster, or sexual violence [1]. Using DSM-V criteria, global estimates of lifetime prevalence range from 1.3% [2] to 8.8% [3], and the illness causes a considerable public health and economic burden [4, 5]. Successful first-line psychotherapeutic treatment options for PTSD include cognitive behavioral approaches and eye movement desensitization and reprocessing (EMDR) [6, 7, 8]. Options for pharmacotherapy include selective serotonin reuptake inhibitors, which have shown success in reducing PTSD symptoms but are not considered as effective as psychotherapy [9, 10]. Critically, a portion of individuals remain non-responsive to both forms of intervention [11, 12, 13, 14, 15], and this has motivated researchers to develop other treatment options [16, 17, 18].

A promising candidate for drug-assisted psychotherapy is 3,4-methylenedioxymethamphetamine (MDMA), a ring-substituted amphetamine

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[19]. This drug possesses unique psychoactive and mildly hallucinogenic properties, causing users to feel euphoria, increased intimacy, and empathy [20, 21, 22, 23]. These psychoactive effects make MDMA a popular drug for recreational use [24, 25], and it is illicitly sold under slang names such as "ecstasy" and "Molly". Because MDMA is classified as a Schedule I controlled substance, the application for MDMA use in treatment for PTSD therapies has been controversial [17]. However, researchers have launched efforts to meet such challenges–the Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit organization dedicated to researching and developing the therapeutic potential of psychoactive drugs [26]. Researchers collaborating with MAPS have completed the first clinical trials testing the efficacy of MDMA-assisted psychotherapy. In the following review, I will provide an outline of these clinical trials, highlight the potential limitations to the studies, and point out future topics for exploration. Also, I will attempt to provide a balanced view of the long-term negative sequelae associated with MDMA use.

2. Psychoactive Effects of MDMA

MDMA produces a suite of unique psychoactive effects, including positive mood, increased arousal, and greater empathy. This last quality places the drug within the class of enactogens–psychoactive agents that heighten feelings of intimacy, sociability and communication [16, 17, 18, 19]. Researchers hypothesize that MDMA induces such changes by increasing levels of serotonin and–to a lesser degree–norepinephrine and dopamine [27, 28]. This perhaps results in increased emotional tolerance when addressing traumatic experiences and memories [29, 30]. Additionally, MDMA has been found to elevate serum oxytocin, a neurohormone associated with social affiliation and facilitation of interpersonal trust [31, 32]. However, it is unclear whether this elevation in oxytocin actually contributes to the subjective effects of MDMA as several studies have found no association [33, 34]. Brain imaging in humans has revealed that MDMA also attenuates perceptions of threat by decreasing activity in the left amygdala [35]. Combined, these positive subjective effects seem to make MDMA a powerful adjunct for therapy. However, MDMA also produces effects that may be counterproductive towards therapeutic intervention. The 5-6 hour "high" experienced with MDMA is followed by a period of neurochemical depletion characterized by low mood and lethargy [36, 37]. And while the drug can help reduce anxiety regarding social interaction [38], numerous studies report that the drug can actually increase general anxiety, an effect common to other stimulants [39]. Despite such drawbacks, several clinical trials have found that MDMA-assisted psychotherapy can help decrease PTSD symptoms in individuals resistant to other treatment approaches [40, 41].

3. MDMA as a Therapeutic Adjunct

Prior to its classification as an illegal substance in the 1980s, MDMA was subject to growing interest in its potential therapeutic use. Alexander Shulgin, a pioneer in the field of experimental psychedelic research, promoted its seemingly beneficial psychedelic effects, which led to its wide application by clinicians and therapists [16]. Prominent

therapists Greer and Tolbert conducted MDMA-aided music therapy sessions, notably highlighting both the positive and negative effects experienced by their patients [42]. In a typical session, 75-150 mg of MDMA was administered to an informed volunteer and sometimes followed up with a smaller dose to prolong the effects of the drug. From these case studies, it was hypothesized that MDMA helped extinguish feelings of fear, allowing the participants to become more comfortable communicating traumatic experiences. Researchers have emphasized that the psychotherapeutic component of this treatment should not be overlooked–they argue that it is the interaction of MDMA with therapy that produces enduring results, not simply administration of the drug itself [29]. While the criminalization of MDMA largely halted such therapeutic studies for more than decade [30], the growing need for PTSD treatment alternatives has motivated current research to investigate the safety and efficacy of MDMA as a therapeutic adjunct.

4. MDMA Clinical Trials for PTSD

In 2008, Bouso et al. carried out the world's first government approved clinical trial designed to test the safety and efficacy of MDMA-assisted therapy [43]. Funded by MAPS, the study planned to administer relatively low doses (50 or 75 mg) of the drug to a small sample of women with chronic PTSD. Originally, the double-blind, randomized trial included 29 women, but political pressure led to the cancellation of the study when only 6 subjects had been treated, making it difficult to conduct meaningful statistical analysis. All participants who had been dosed with MDMA ($n = 4$) during therapy showed higher improvement than those given placebo ($n = 2$), with greatest PTSD symptom reduction seen in the single individual given the highest dose of MDMA (75 mg) and intermediate symptom reduction in the three individuals given a slightly lower dose (50 mg). Though limited by the small sample size, these findings indicated that administration of MDMA in conjunction with psychotherapy could be conducive to PTSD treatment.

A key paper by Mithoefer et al. [40] confirmed the findings of the Bouso et al. [43] study, while presenting an appreciably larger sample size. Also sponsored by MAPS, this American study employed a similar double-blind methodology, assigning 20 participants (14 female / 3 male) to either an MDMA group ($n = 12$) or a placebo group ($n = 8$). The experimental sessions, which included a balance of quiet introspection and therapeutic discussion, were 8-10 hours long and were ended by an overnight stay so health condition could be monitored. The dosage of MDMA in this study was considerably higher than the earlier study–at least 125 mg of MDMA was administered to each participant in the MDMA group. Thus, participants experienced more noticeable side effects, including elevations in blood pressure, heart rate, and body temperature. Critically, this undermined the double-blinded aspect of the study design: both participants and therapists easily recognized whether the sessions were medicated with drug or placebo. Elevated physiological measures seemed to reduce to baseline at the end of each session, and although some participants reported jaw tightness, nausea, loss of appetite, and impaired balance, the side effects were not serious or long-lasting. Neurocognitive tests conducted two months after the experimental sessions revealed

that MDMA intake did not have adverse effects on cognition. The researchers found that PTSD symptoms decreased for both the experimental and placebo groups, but the MDMA-administered group showed significantly greater improvement, with a symptom reduction of 83.3% compared to 25% (placebo) two months after the experimental sessions. Later, when the blind was removed and placebo participants were given the option to partake in MDMA-assisted therapy sessions, they saw similar levels of improvement.

To determine if these results would be consistently maintained, the researchers also conducted a long-term follow-up around 3.5 years after their original study's exit date [44]. All subjects who received concurrent MDMA administration and psychotherapy were enrolled in this follow-up. PTSD symptoms did not show a statistical increase during this period, demonstrating that participants saw a retained improvement after MDMA-assisted therapy. Additionally, all participants reported that the experience had imparted some degree of benefit on their lives. None of them reported any harm or dependence issues after taking MDMA, nor did they self-report any evidence of neurocognitive decline. However, one participant did admit to taking MDMA again in a "quasi-therapeutic" environment as an attempt to recreate the effect of the experimental sessions. This type of self-medication may be concerning, and its implications are discussed later. Additionally, while there was a lack of evidence for cognitive decline, objective assessments were not used to confirm the participants' favourable self-reports. The researchers also pointed out a major confounding factor–out of the 19 subjects enrolled in the follow-up, 8 were still in psychotherapy and 12 were taking psychiatric medications. This may have played a role in sustained symptom improvement, but the small sample size prevented statistical comparison between individuals who were undergoing continued treatment and those who were not. Despite its limitations, this follow-up demonstrated the promising treatment durability of MDMA-assisted psychotherapy.

In 2013, Oehen et al. [41] attempted to replicate the findings of the Mithoefer et al. [40] study. To increase the strength of the double-blind design, an "active" placebo of 25 mg MDMA was used (producing similar but milder effects compared to the 125 mg dose). Again, MDMA showed no serious adverse health effects when administered in a clinical setting. However, even though the full-dose group showed a decrease in PTSD symptoms as compared to the "active" placebo group (which showed no symptom reductions), the effect was not statistically significant. On average, those given the full-dose of MDMA saw symptom scores decrease by only 23.5%, a marked difference to the original 83.3% decrease found by Mithoefer et al. The researchers suggested cultural differences, therapist differences, and uneven sampling as potential explanations for these discrepancies.

Currently, MAPS has several ongoing clinical studies underway. In October 2016, researchers in the U.S. completed a study involving American veterans, firefighters, and police officers with chronic, treatment-resistant PTSD [45]. Additionally, a small, pilot study in Canada has recently finished experimental sessions [46]. The publication of these results will help determine whether MDMA-assisted therapy yields statistically significant PTSD symptom reductions.

5. Possibility of Adverse Health Sequelae

The short-term effects of MDMA are well-characterized in a clinical setting. Most dosages range from 0.75-1.5 mg MDMA/ kg body weight (up to 150 mg per session) and can cause elevations in body temperature, heart rate, and blood pressure [21, 23, 27]. Participants of such studies have reported adverse effects such as nausea, anxiety, tight jaw, and loss of appetite [40, 41, 47]. Importantly, these effects seem to be tolerable and do not last beyond several days [40, 41, 47].

While the MAPS-sponsored clinical trials showed a lack of persisting adverse health effects in participants [40, 41, 44], there is a large body of research associating MDMA with various long-term harms [36, 48, 49, 50, 51, 52, 53]. The drug has been linked to psychiatric distress, cognitive decline, and neurotoxicity [36, 51, 52, 53]. However, much of this research has been done in vitro, in animal models, or in a naturalistic or retrospective manner on drug users [36, 48, 49, 50, 51, 52, 53, 54, 55]. It remains a challenge to parse out whether these findings remain relevant to MDMA use in a clinical psychotherapeutic setting.

Studies conducted on drug users have found that MDMA may be implicated in a range of adverse psychological effects such as impaired cognition [37, 56] and sleep quality [52, 57]. At least one study has linked MDMA use with downstream depressive symptoms [39], but other research has not confirmed these findings [58, 59]. Thus, our understanding of negative psychological consequences remains equivocal. Common criticism for research done on drug users is that it fails to account for polydrug use and ignores the unpredictable composition of "ecstasy" [55, 60], the recreational form of MDMA which often contains adulterants that range from benign fillers to other illicit psychoactive substances [61, 62, 63]. Controlling for polydrug use, a 2014 retrospective study with a considerable sample size ($n = 997$) found that ecstasy polydrug users struggled more with impaired memory and sleep, increased impulsiveness, and greater prevalence of depression, in comparison to non-ecstasy polydrug users [50]. Despite rigorous controls for various polydrug use, this study is still limited by potential sampling bias and the questionable content of ecstasy tablets.

A range of in vitro, animal, and drug user studies have associated MDMA with neurotoxicity [49, 53, 64]. However, it is not clear whether these potential harms are applicable to the context of MDMA-assisted psychotherapy, where the dosage of the drug may be considerably lower, and the treatment consists of only a few medicated sessions [65]. Again, the confounding factors of polydrug use and potential adulteration of ecstasy come into play when interpreting research done on ecstasy drug users. Even so, a recent review of neuroimaging studies done on moderate ecstasy users in fact showed no evidence of associated structural or functional brain alterations [66]. Many questions about possible long-term adverse effects remain unresolved, and additional randomized studies in humans are necessary before further conclusions can be drawn.

6. Potential for Drug Abuse

The possibilities of abuse and dependence must be fully elucidated if MDMA is to be submitted for clinical application. It is not fully understood whether the drug

is physically addictive [67, 68, 69]. In animal studies, rats have been found to self-administer MDMA [70], though the motivation to do so is lesser compared to other drugs such as cocaine [71]. When generalizing such studies to humans, additional factors such as polydrug use and mental illness may complicate our understanding. In a case study report, Jansen [72] noted several situations where MDMA use met the criteria for substance dependence. One of the subjects in this case report had a PTSD diagnosis and was taking up to 25-30 tablets of MDMA every weekend as a way to alleviate emotional numbing and increase feelings of social empathy. His use of MDMA had caused him to critically neglect his financial livelihood as he had resorted to selling personal belongings to buy MDMA. Though a case like this illustrates an extreme, it demonstrates a potential complication for MDMA-assisted therapy. But perhaps, a more realistic scenario of potential abuse is brought to light by the study participant who reported seeking MDMA in a quasi-experimental setting outside of the study [44]. This type of self-medication may pose risks since health professionals are not present to monitor physiological condition. Also, if this behavior is repeated, it may lead to a pattern of abuse unconducive to the purpose of the treatment.

7. Study Limitations and Future Directions

The weakness of the double-blinded methodology in the Mithoefer et al. [40] study was a notable limitation. However, it is hard to determine if this factor confounded the results in any way. In the Oehen et al. [41] study, the blinding method was improved by replacing the placebo group with an active placebo group, whose participants received enough MDMA (25 mg) to produce some of the drug effects, but not enough to successfully aid treatment. Indeed, PTSD symptom scores actually saw a slight, non-significant increase in this group.

Another major limitation found across many of the studies is the disproportionate gender ratio of the participants–all the participants in the Bouso et al. [43] study and a majority of participants in the Mithoefer et al. [40] and Oehen et al. [41] studies were female. This may have played a role in the treatment success as the psychoactive effects of MDMA have been found to be more intense in women than men [73]. Critically, the participants in the U.S. veterans study [45] are mostly male, and publication of these results may help explore potential sex differences and increase the generalizability of the current results.

So far, MDMA-assisted PTSD therapy has not employed gold-standard psychotherapy approaches such as cognitive behavioural therapy or EMDR. MAPS plans to pilot a MDMA-assisted therapy trial integrating cognitive behavioural conjoint therapy [74]. Given the success of cognitive behavioural approaches [6, 7, 8], such directions are of great interest.

Notably, all MDMA-assisted PTSD therapy trials have been funded by the same source. Lack of funding from separate government and pharmaceutical agencies may be justified by the controversial nature of psychoactive drug research as well as the expired patent on MDMA. However, in the future, it may be helpful to see PTSD symptom reductions confirmed by research unassociated with MAPS.

8. Conclusion

Within the past decade, important findings have suggested the efficacy of MDMA as a therapy adjunct for individuals living with treatment-resistant PTSD. The therapeutic potential of this enactogen stems from its ability to elevate mood, enhance trust, and reduce perception of threats. However, our knowledge of long-term adverse effects is inconclusive. Although research has often associated MDMA with harmful sequelae such as psychiatric distress, cognitive decline, and neurotoxicity, the relevance of these studies in a psychotherapeutic context is debatable. Several MAPS clinical trials are either ongoing or awaiting publication. If the promising initial results of MDMA-assisted psychotherapy are confirmed, this treatment option may offer a transformative experience for individuals living with treatment-resistant PTSD.

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