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The use of 3,4-Methylenedioxymethamphetamine (MDMA) in the treatment of Post-Traumatic Stress Disorder (PTSD) - review

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Abstract

Introduction: Post-traumatic stress disorder (PTSD) is a common health issue of complex etiology significantly deteriorating functioning in everyday life. It may develop as a result of exposure to traumatic events like traffic accidents, war experience, sexual abuse and domestic violence. Current methods of treatment consist of trauma-oriented psychotherapy supported by selective serotonin reuptake inhibitors (SSRIs). Their efficacy is far from satisfactory thus a search for alternative methods is necessary. 3,4-Methylenedioxymethamphetamine (MDMA) commonly known as “ecstasy” seems to have promising results in the treatment of PTSD.

Aim of study: Review of current knowledge about MDMA-assisted therapy in PTSD, its possible mechanisms of action, efficacy and safety.

Methods and materials: A review of chosen literature from in PubMed database, GoogleScholar database in the years 2000-2023 was conducted using the following keywords: “PTSD epidemiology”, “PTSD pathophysiology”, “PTSD neural activity”, “PTSD brain activity”, “MDMA PTSD”, “MDMA brain activity”, “MDMA neural activity”, “MDMA neurotoxicity”, “MDMA PTSD therapy”, “MDMA safety”, “MDMA caffeine”

Results: MDMA-assisted therapy has promising effects in PTSD treatment and its safety profile is satisfactory. The improvement in symptoms occurs most likely due to its modulating activity on brain structures responsible for threat detection and emotion processing.

Conclusions: Further research is necessary to assess MDMA-assisted therapy in PTSD, especially direct comparison of its efficacy versus first-line treatment SSRIs and assessment of its long-term-safety.

Keywords: “PTSD”, “MDMA”, “PTSD treatment”, “PTSD MDMA”, “MDMA treatment”, “MDMA in medicine”

Introduction

According to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Post-traumatic stress disorder (PTSD) is nowadays diagnosed among patients who had been exposed to or threatened with death, serious injury or sexual violence or had witnessed the traumatic events (once or repeatedly) and present symptoms of recurrent, involuntary memories, dreams, dissociative reactions, physiological distress at exposure to cues that resemble the traumatic event, avoid the stimuli associated with them, have negative alterations in cognition and mood, marked alterations in arousal and reactivity associated with the traumatic events that last at least for 1 month and cannot be attributed to any other medical condition. It is a disturbance causing a significant impairment in social, occupational and other important areas of functioning.¹ The lifetime prevalence rate of PTSD is approximately 5–8%, reaching 17.1% in military personnel, and occurs twice more often in women than in men.^{2,3} Current treatment options include both non-pharmacological and pharmacological strategies. Non-pharmacological strategies rely on:

- Individual, manualized trauma-focused psychotherapy, 12–20, 60-minute sessions weekly, as main and first line treatment for treatment of PTSD,
- Cognitive Processing Therapy (CPT),
- Eye Movement Desensitization and Restructuring (EMDR),
- Written Exposure Therapy (WET),
- Narrative Exposure Therapy (NET),
- Prolonged Exposure (PE).⁴

Although these strategies are considered the gold standard for PTSD treatment many patients undergoing them still present with severe symptoms or drop out of their treatment. In the pharmacological strategy the first-line medications are the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine. However, about 50% of patients do not benefit from the therapy.⁵⁶ Therefore the search for more effective, alternative strategies is crucial. One of the substances possibly being effective in this indication is 3,4-Methylenedioxymethamphetamine (MDMA).

Neural activity alterations in PTSD

At the root of PTSD lies the permanent alteration of brain functioning caused by trauma, resulting in impaired emotional processing and regulation, cognition and other aspects of life. It is impossible to point out one particular structure or circuit whose dysfunction is responsible for PTSD, as the changes in brain activity vary among patients suffering from this disease. Studies have shown that the impacted areas are the precuneus, posterior cingulate cortex (PCC), anterior cingulate cortex (ACC), insula, prefrontal and frontoparietal regions, as well as the hippocampus and amygdala. It suggests the involvement of brain circuits responsible for self-referential processing, salient autobiographical memory, fear and emotion.⁷

MDMA – history

MDMA, commonly known as “ecstasy” is a compound derived from methamphetamine synthesized by the German pharmaceutical company Merck in Darmstadt in 1912. The research leading to the creation of MDMA was, surprisingly, aimed at developing hemostatic substances. For many years it was studied by the company but has never been applied to any clinical use. In 1970 it was detected for the first time in tablets seized in Chicago and in the early 1980s became popular as a drug commonly used at dance parties and “raves”. Until 1988 became a Schedule I controlled substance in United States and most other countries.⁸

MDMA – mechanism of action

MDMA belongs to a group of substances called “empathogens”. It means it creates a feeling of emotional communion and openness, increased sociability and decreased defensiveness.⁹ The “pro-social” behavior is associated with the activation of serotonin 1B (5-HT_{1B}) receptor in nucleus accumbens (NAc), one of the structures involved in the reward system. 5-HT_{1B} receptor controls the activity of serotonin transporter (SERT) whose blockage leads to impaired serotonin (5-HT) reuptake and activation of neural circuits associated with trust and social engagement.¹¹ This is a unique feature among psychedelics because other substances like lysergic acid diethylamide (LSD) or psilocybin mostly mimic the endogenic serotonin molecule presenting higher affinity to serotonin 2A receptor.¹⁰ Because of the methamphetamine component MDMA also provokes the release of dopamine and inhibits the reuptake of this molecule from the synaptic cleft increasing the dopaminergic tone and therefore creating a feeling of stimulation, alertness, excitation and motivation in people taking the drug.¹¹ However, unlike amphetamines, MDMA causes 5-fold higher increase in serotonergic than dopaminergic transmission.¹² Altogether, elevation of both neurotransmitters

makes people under the influence of MDMA have more energy, without being irritated, and feel a lot of pleasure and emotional warmth which results in producing a state of motivation for social engagement, and parallelly, feeling of being rewarded for the interaction.¹³ One study shows that even octopuses presents more social behavior after the administration of MDMA. In the trial the animals tended to spend more time with each other.¹⁴ This finding may seem far-fetched however the paper proved the existence of already mentioned SERT in the abovementioned animals. MDMA alters the brain functioning not only at the molecular level but also influences the activity of particular brain regions. Study done by Gillinder Bedi et al. showed a significant attenuation of amygdala activation in participants under MDMA influence when they were shown pictures of angry faces in comparison to subjects being administered with placebo. At the same time, the group receiving MDMA perceived the angry faces as less angry. Moreover, the substance caused more significant activation of ventral striatum in response to happy facial expressions and consequently participants described the happy faces as even happier.¹⁵ Another studies focused on cerebral blood flow (CBF) and functional connectivity (FC) concluded that MDMA alters functioning of many brain structures but the most significant changes were observed in decreased CBF in amygdala and hippocampus which correlated with the subjective effects of MDMA. Moreover, amygdala-insula FC diminished in the long-term and amygdala-hippocampus FC increased after MDMA consumption and correlated positively with improvements in PTSD symptoms.^{7,12}

MDMA-assisted therapy

There is evidence suggesting the efficacy of MDMA-assisted therapy in PTSD. In a trial done by Mitchell et al.⁵ 90 participants were divided to two groups: one received MDMA assisted therapy and the second therapy with placebo. The average duration of PTSD diagnosis was 14.8 years and 13.2 years in the MDMA and placebo groups respectively. The volunteers were subjected to three 8-hour long experimental sessions of MDMA-assisted therapy or therapy with placebo, spaced 4-weeks apart, preceded with three preparatory sessions with a team of two psychotherapists. . The severity of symptoms was measured with Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and functional impairment was measured with the Sheehan Disability Scale (SDS) at the beginning and after each exposure to the substance. Participants received a dose of 80-180mg of MDMA in each experimental session divided to initial and supplemental dose. Each administration was followed by 90 minutes long integration session. Before every part of the treatment participants were tested for drugs in their system,

pregnancy in case of women, had their blood pressure, body temperature and heart rate taken. MDMA-assisted therapy significantly attenuated symptoms comparing CAPS-5 score at the baseline and 18-weeks after. The average decrease was -24.4 in the experimental group and -13.9 in the control group. At the same time, SDS score diminished by -3.1 and -2.0 in the experimental and control group respectively. Comorbidities like dissociative subtype of PTSD, depression, history of alcohol abuse did not affect the benefits of the therapy. 67% of the patients in the MDMA group did not meet diagnostic criteria for PTSD at the end of the treatment compared with only 32% in the placebo group. In addition, 33% of the experimental group met criteria for remission while only 5% of the placebo group. MDMA had approximately two-fold higher efficacy in symptom reduction than sertraline and three-times higher efficacy than paroxetine, however direct comparison of MDMA-assisted therapy with SSRIs for PTSD would be necessary.¹⁶ Symptoms of depression were also tracked in the trial with Beck Depression Inventory II (BDI-II) being reduced in the MDMA group by -19.7 and -10.8 in placebo group. MDMA often caused a transient increase in blood pressure, however did not potentiate the risk of severe adverse reactions neither abuse potential, cardiovascular risk nor suicidality. MDMA seems to have similar or even better safety profile than first-line SSRIs.¹⁷

Study by Christopher R. Nicholas¹⁸ strongly suggests that MDMA-assisted therapy may contribute to decreased alcohol consumption among patients with PTSD and does not raise the risk of illicit drugs use. The fact needing emphasis is that although MDMA has promising effects in therapy of PTSD it does not help the patient on its own. It is only in combination with talk therapy understood as aforementioned psychotherapy, CPT or NET that the positive outcomes occur.⁵

Neurotoxicity

There are numerous studies both in laboratory animals and humans suggesting the destructive influence of MDMA on brain performance resulting in impaired cognition, memory and learning.^{19,20} Most of them focus on the 5-HT system and the possible toxicity of its extensive activation. However, these results are highly vulnerable to methodological limitations which may bias their findings. Firstly, many of them are observational studies that compare non-users with people with a long history of illicit drug use, not only MDMA but also cannabis, amphetamine, other hallucinogens and cocaine.^{21,22} Therefore it is impossible to extract the damage done by MDMA from other substances especially as the “ecstasy” pills sold on the “street” may contain much less or even no MDMA and be adulterated with compounds such

as methamphetamine which is known to be neurotoxic.^{23,24} Secondly, non-user participants of many studies were not members of the “rave” culture and thus were not exposed to sleep and fluid deprivation from all-night dancing which may produce cognitive defects itself.²⁵ Thirdly, participants were rarely screened for drugs and alcohol use on the day of testing. Lastly, studied populations were not homogenous in terms of intelligence, social status, financial situation – factors that may significantly interfere with findings. Study performed by John H. Halpern et al.²⁶ published in 2011 takes into consideration all the limitations listed above. The study failed to present significant differences between MDMA users and non-users in cognitive performance, apart from poorer strategic-self-regulation, possibly reflecting increased impulsivity. Other studies suggest that high doses (more than 3 mg/kg) produce amnesia and addiction but at the same time find little evidence that the amount of the substance usually used in clinical studies (approximately 1-2 mg/kg) can cause side effects.²⁷ It has been shown in mice that simultaneous administration of MDMA and caffeine significantly increases neurotoxicity and mortality among these animals.²⁸ MDMA is a psychostimulant and therefore may produce increases in blood pressure, body temperature or heart rate – symptoms that combined with other factors like sleep deprivation, electrolyte deficiencies, for example during all-night dance parties, have a higher potential to generate adverse events. It points to the fact that the hazards of MDMA depend on the setting it is being administered in and its dosage. Provided that appropriate conditions are maintained, MDMA seems to have a larger than satisfactory safety profile.

Conclusions

MDMA-assisted therapy in PTSD is a new approach to treatment of this highly debilitating disease against which modern medicine is often helpless. By altering activity of certain brain structures and circuits responsible for threat detection, emotion processing and memory consolidation MDMA may develop new attitude to the trauma in patients with PTSD and alleviate their symptoms. Further research is necessary to assess its effectiveness and safety as well as possible long-term side effects. A debate on legal regulations is also mandatory to facilitate use of MDMA in clinical trials and thus accelerating the research.

Author's contribution: All authors contributed to the article. Conceptualization – Karol Womperski, Justyna Woźniak; methodology - Inga Magda; check - Magdalena Gaik, Ewa Uram; formal analysis – Magdalena Osuch; investigation – Inga Magda; resources – Rafał Bogacz; data curation – Justyna Woźniak; writing - rough preparation – Ewa Uram, Magdalena Osuch; writing - review and editing - Karol Womperski, Justyna Woźniak; visualization – Rafał Bogacz; supervision - Inga Magda; project administration – Magdalena Gaik. All authors have read and agreed with the published version of the manuscript.

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