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Will MDMA-assisted psychotherapy become a breakthrough in treatment-resistant post-traumatic stress disorder? A critical narrative review.

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Summary

Post-traumatic stress disorder (PTSD) is a common mental health condition that begins after exposure to a traumatic event. Despite recommended various therapeutic approaches, including both pharmacotherapy and psychotherapy, treatment is not as effective as expected. Over recent years the pharmaceutical industry has not been able to offer a new approach, founded on multiple mechanisms of action. That is why a part of researchers focused on psychoactive substances synthesized years ago and then banned. These days MDMA-assisted psychotherapy for the treatment of PTSD clinical trials are conducted, and due to previous results, the Food and Drug Administration (FDA) granted a breakthrough therapy designation. In this article, we present the mechanism of actions, the therapeutic rationale, applied psychotherapeutic methods, and potential dangers. If ongoing phase 3 studies are completed and clinical efficacy criteria are achieved, the FDA could approve the treatment as early as 2022.

Key words: PTSD, MDMA, psychotherapy

Introduction

Methylenedioxymethamphetamine (MDMA), classified as an entactogen for its unique effects related to greater social attachment, closeness and empathy, was synthesized in the early 20th century by Merck pharmaceutical company as an intermediate for the production of a hemostatic drug. The compound gained more attention in the scientific world over half of century later, when in the 1970s Alexander Shulgin and David Nicholson published the first results of their research on how

this substance affects the human body. Shulgin, noticing the healing potential in MDMA, decided to introduce it to a psychotherapist who used psychedelic substances in his practice, Leo Zeff, who began to use this compound in practice. Sometimes it is mistakenly assumed that this substance was banned in 1985 due to numerous incidents that were dangerous to the life and health of patients, while these measures were taken to prevent potential access to 3,4-methylenedioxyamphetamine (MDA), the production intermediate of which MDMA is. 21st century brought some changes by the Multidisciplinary Association for Psychedelic Studies (MAPS), a non-profit organization focusing its activities on the use of psychoactive substances in medicine, and a return to research on the psychotherapeutic potential of methylenedioxymethamphetamine [1].

Aim

The aim of this paper is to sum up available information about mechanism of action, effectiveness and safety of methylenedioxymethamphetamine (MDMA) used in the treatment of treatment-resistance post-traumatic stress disorder (PTSD).

Material and method

This article was prepared based on scientific publications in English available in the PubMed database, published in 2000–2020. The searched phrases included: "MDMA-assisted psychotherapy", "MDMA mechanism of action" as well as "MDMA and PTSD". Then, on the basis of abstracts, we pre-selected the articles and analyzed the collected material together with citations included in the references. Additionally, we added the professional literature and the latest information extended from the organization conducting clinical trials of MDMA-assisted therapy used in treatment-resistant post-traumatic stress disorder – Multidisciplinary Association for Psychedelic Studies (MAPS).

Mechanisms promoting the therapeutic effectiveness of methylenedioxymethamphetamine

MDMA has a complex and multi-directional mechanism of action. Due to the ability to cross the blood-brain barrier, this compound affects various receptors. It is characterized by affinity for the dopamine, noradrenaline and (the strongest) serotonin transporters. This substance also binds directly to α2-adrenergic, serotonin, histamine, β-adrenergic as well as dopamine D1 and D2 receptors. The effect of this substance on the levels of other hormones in the body, such as prolactin, oxytocin, cortisol, ACTH, and AVP, cannot be overlooked [2].

The main post-exposure effect of methylenedioxymethamphetamine is associated with an increase in the concentration of serotonin in the extracellular space. This is done by two mechanisms: increasing the release of serotonin and preventing its reuptake. The effect on serotonin 5-HT1A and 5-HT1B receptors is associated with the occurrence of an increased sense of self-confidence in the patient, as well as a reduction in the perceived level of anxiety and depressive symptoms, while interaction with 5-HT2A receptors causes narcotic effects.

Moreover, based on studies conducted in an animal model, 5-HT1A receptors are responsible for increasing the concentration of oxytocin in the brain; when a receptor antagonist was administered, the secretion of oxytocin was blocked. Oxytocin release appears to be crucial for several reasons. According to a recently published study, a single dose of MDMA is able to extend the time during which oxytocin regulates synaptic plasticity within the nucleus accumbens [3]. This area of the brain, which is rich in neurons with high expression of dopaminergic receptors, plays an important role in the control of impulsive and emotional functions. In the context of sleep disorders occurring in people with PTSD, it seems important that part of this nucleus is involved in inducing the deep sleep phase [4]. Also, the increase in empathy, closeness, trust, and a tendency to prosocial behaviors that are desirable in a therapeutic context after exposure to MDMA is probably related to the increase in the level of oxytocin [2, 5].

Although it is still unclear to what extent the dopaminergic system mediates acute adverse effects occurring after taking MDMA in humans, it is the elevation of norepinephrine and dopamine concentration that seems to contribute to the patient's increased level of consciousness and arousal [2, 6], which may also turn out to be helpful in treatment, motivating the patient to become more involved in the whole process. On the one hand, the literature reports a significant reduction of the positive post-exposure effects after pharmacological inhibition of D2 receptors with haloperidol, and on the other hand, genetic studies investigating the influence of inter-individual genetic diversity within the dopaminergic system do not show that it has a significant impact on the occurrence of different intensity of the effects after taking methylenedioxymethamphetamine [7]. Undoubtedly, further work in this area is needed.

Potential mechanisms behind therapeutic efficacy of MDMA also include the enhancement of fear extinction, which is the neurobehavioral basis of the efficacy of prolonged exposure therapy used in the treatment of PTSD. It is possible to develop memory extinction when the patient exposed to an unpleasant stimulus (e.g., an illustration, photo or film) begins to feel fear, but is able to withstand it. In this case, there is no direct blurring of the memory trace associated with the perceived fear, but a new memory trail. The repetition of this action consequently leads to a gradual disappearance of the conditional response. The improvement in this matter is probably possible due to the increased release of norepinephrine and cortisol [2, 8–9]. Another

compound that participates in the potentiation of extinction is possibly the brain-derived neurotrophic factor (BDNF) belonging to the family of nerve growth factors. The appropriate concentration of BDNF is necessary for MDMA to induce gene expression in the amygdala and prefrontal cortex [10]. Recalling negative memories in PTSD patients may be associated with a less severe fear also due to reduced blood flow in the hippocampus and right amygdala [11].

The effects of MDMA exposure within the brain have been demonstrated many times in neuroimaging techniques. In the conducted studies, changes in activity were observed within two brain structures important for the functioning in society – an increase was marked in the prefrontal cortex, while a decrease in the amygdala [11]. Considering their importance, as well as the existence of completely different deviations in activity in PTSD patients, this seems to be another valuable therapeutic effect [12–14].

MDMA-assisted therapy

Post-traumatic stress disorder is a disorder that poses a challenge for researchers looking for new, more effective therapeutic options. The currently used first-line drugs often do not bring the expected results, therefore methylenedioxymethamphetamine is considered as a potential drug due to the effects closely related to the reduction of PTSD symptoms, which, together with neurobiological correlates, are included in Table 1 [2].

Table 1. **A summary of how the effects of MDMA are related to the treatment of PTSD symptoms, with associated neurophysiological correlates**

MDMA effects	Postulation of how MDMA effects relate to the treatment of symptoms associated with PTSD	Neurobiological correlates
Reduces depression and anxiety	Provides patient with an experience of positive mood and reduced anxiety in which to engage in therapy	Release of pre-synaptic 5-hydroxytryptamine at 5-HT1A and 5-HT1B receptors
Stimulates alterations in the perceptions of meaning	Provides patient with an opportunity to see old problems in a new light	Increased activity at the 5-HT2A receptors
Raises levels of arousal	Stimulating effect increases motivation to engage in therapy	Release of dopamine and noradrenaline
Increases relaxation	Reduces hypervigilance associated with PTSD	Increased alpha 2-adrenoceptor activity
Improves fear extinction learning	Allows patient to reflect upon traumatic memories during psychotherapy without being overwhelmed	Release of noradrenaline and cortisol

table continued on the next page

Increases emotional attachment and increases feelings of trust and empathy	Improved relationship between patient and therapist. Provides patient with capacity to reflect on traumatic memories	Multiple factors, including release of oxytocin
More likely to use words relating to friendship, support and intimacy	improve the relationship between the patient and the therapist, which can generate discussion about wider aspects of patient's social and emotional relationships	Multiple factors, including release of oxytocin
Produces reduced social exclusion phenomena	Opportunity to reflect upon patients' wider social functioning	Multiple factors, including release of oxytocin
Improved detection of happy faces and reduced detection of negative facial expressions	Enhances levels of shared empathy and pro-social functioning	Increased PFC activation and decreased amygdala
Reduced subjective fear response on recall of negative memories	Opportunity to reflect upon painful memories of trauma during psychotherapy	Decreased cerebral blood flow in the right amygdala and hippocampus

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In the trials conducted so far by MAPS , patients were randomly assigned to two groups participating in the same intensive psychotherapy and receiving different doses of methylenedioxymethamphetamine. The control group received 0 mg, 25 mg, 30 mg or 40 mg of MDMA, while the study group received 75 mg, 100 mg or 125 mg of MDMA. These doses were taken in two or three treatment sessions 3 to 5 weeks apart.

In the conducted studies, psychotherapy was associated with carrying out a few preparatory sessions without substance use and many sessions that aimed to integrate MDMA experiences. Every meeting, the duration of which was from 5 to 8 hours, was conducted in esthetic, comfortable patient rooms with the participation of two cognitive behavioral therapists of both genders, trained for carrying out such a process, who acted in accordance with instructions developed by MAPS [15]. In addition, while taking MDMA, participants were often encouraged by professionals to lie down and close their eyes. During this time, they received headphones with appropriately selected music, the purpose of which was to strengthen the therapeutic process.

In 2019, the results of the second phase studies, carried out in the years 2004–2017, were published, indicating a 56% effectiveness of this treatment in the PTSD scale in the form of a clinical interview for DSM-IV (CAPS-IV) compared to 23% effectiveness in the control group. Re-examinations carried out 12 months after the end of therapy showed an increase in the number of participants who no longer met the PTSD criteria

to 67% (n = 91) [16]. According to the data, patients' condition improved from one month to two months after MDMA-assisted psychotherapy. A long-term analysis of the participants of these studies proved that the reduction in the severity of the symptoms of post-traumatic stress disorder lasts from one year to 3.8 years [16].

Taking into consideration the clinical results gathered so far, the FDA recognized this therapy as a breakthrough in 2017. Such a decision is made by the FDA in the case of substances assigned to health conditions that significantly threaten the life of patients, for which the agents currently available on the market show relatively low effectiveness.

Potential risk

Neurotoxicity is an issue frequently raised in the context of methylenedioxymethamphetamine. Studies carried out on animal models indicated a toxic effect on nerve cells, however, the authors of later published papers pointed out to a number of methodological errors made in those studies, among others, related to interspecies differences in pharmacokinetics, or maladjustment of the applied dose [17–18]. Moreover, a trial with rodent weight-adjusted amounts of the psychoactive agent, equivalent to that used in humans, showed no changes in genes associated with neuronal damage. However, studies informing about the occurrence of post-exposure oxidative stress should not be ignored [19]. Prolonged oxidative stress leads to the formation of irreversible changes in the cell, leading it consequently to the apoptotic pathway. The brain, due to the dense presence of lipid cells, is particularly susceptible to the harmful effects of pro-oxidative compounds. The authors associate oxidative stress with damage to the blood-brain barrier, which in turn leads to changes in the morphological structure of the brain and the occurrence of disturbed patterns of neuronal growth [20].

There are many studies in the available literature informing about cognitive dysfunctions occurring after taking ecstasy, including low speed of information processing as well as deficits in verbal or spatial memory [21–23]. Most of these publications are retrospective studies, and some of the respondents have taken the substance more than once. It is also worth noting that in the prospective, long-term study of PTSD patients participating in first phase studies of MDMA-assisted therapy, no deficits in this aspect were noticed [24, 25].

In the context of recreational users, the phenomenon of polytoxicomania should not be overlooked [26]. It is worth mentioning that the risk of MDMA abuse is moderate, lower than in the case of drugs such as cocaine or amphetamine [27].

People who regularly use narcotic drugs are unlikely to consume ecstasy every day, the frequency of use ranges from one to four times a month [28]. There was also a study in which participants with no previous experience with MDMA were given

this compound. As noted, these volunteers did not report their willingness to re-use the substance outside the context of the study [29].

From the point of view of a practitioner, it is also necessary to pay attention to the differences in emotional states prevailing in recreational users and in patients undergoing therapy. The first group of users takes substances to achieve euphoric experiences, while the medical use of methylenedioxymethamphetamine is associated with recalling difficult memories and experiences.

Urine samples were collected from each potential participant during the selection of participants for the pilot study [30]. The activity was repeated during the course of treatment and up to 12 months after its completion in all patients participating in the study, in order to exclude the use of the substance outside the medical context. No metabolites of psychoactive substances were found in urine in any of the users. To date, in all trials conducted for PTSD, only one subject reported later ingestion of the compound outside of the therapeutic context [24]. Reflecting on the various safety aspects of MDMA use, existence of ecstasy of questionable chemical purity should not be ignored [31]. The admixture of even small amounts of 4-methoxyamphetamine (PMA) in an ecstasy tablet may prove fatal [32]. Moreover, the liver damage observed in 16% of recreational users [33], probably resulting from cellular damage and mitochondrial dysfunction caused by increasing oxidative stress [34], was not observed in patients undergoing therapy.

Hyperthermia, partly associated with the increase of IL-1β, and transient changes observed within the cardiovascular system are very dangerous only in unsuitable ambient conditions (poorly ventilated, quickly heating rooms) [33–35] . For these reasons, the juxtaposition of medical complications after exposure to a certain amount of pure MDMA under strictly controlled conditions and street "molly" seems to be inappropriate.

Comparison of sertraline, paroxetine and MDMA

The first-line drugs assigned to the management of PTSD belong to SSRI group – sertraline and paroxetine – which in this particular disorder are characterized by a relatively small, slightly different from placebo, therapeutic effect [36].

The authors of a recently published study compared the safety and effectiveness of MDMA adjuvant therapy with first-line drugs used in PTSD.

The differences in CAPS (Clinician Administered PTSD Scale) scores are presented in Table 2 [36]. The beneficial effects of methylenedioxymethamphetamine-assisted therapy continued to be seen in 67% of participants (n = 91) after 12 months. Long-term efficacy for SSRIs has not been assessed. It is noteworthy that sertraline is not statistically significantly effective in men, while the gender differences in treatment effects are absent with MDMA. On the other hand, according to some studies, women may be more prone to some of the side effects occurring after taking methylenedi-

oxymethamphetamine [29, 37]. Comparing the two types of therapy, we should not forget also that paroxetine and sertraline induced sexual dysfunctions can greatly reduce the quality of life of patients. A summary of side effects of therapy the most frequently reported by patients is presented in Table 2 [36].

Table 2. **Comparison of sertraline, paroxetine and MDMA based on CAPS results and short-term side effects**

	Sertraline	Paroxetine	MDMA
	CAPS-II[a] (sertraline-placebo) dropout [%]	CAPS-II[a] (paroxetine-placebo) dropout [%]	CAPS-IV[b] (MDMA-control) dropout [%]
Study 1	-6.8 effect size 0.31 29.3%	-14 effect size 0.56 35.5%	-26.2 effect size 0.9 7.6%
Study 2	-9,8 effect size 0.37 28.4%	-11 effect size 0.45 39.0%	-
Study 3	-	-6 effect size 0.09 33.0%	-
Short-term side effects (at least 2x of the frequency of placebo/control group)	nausea, headache, insomnia, diarrhea, dry mouth, ejaculation failure, somnolence, dizziness, fatigue	asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, decreased libido, ejaculation failure, female genital disorders, impotence.	anxiety, bruxism, lack of appetite, headache, fainting, diarrhea, difficulty concentrating, dizziness, heavy legs, impaired balance, nausea, nystagmus, paresthesia, sweating, sensitivity to cold, thirst, weakness

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Based on item 36 in the references.

[a]CAPS-II (Clinician-Administered PTSD Scale for DSM-II) PTSD scale in the form of clinical interview for DSM-II

[b]CAPS-IV (Clinician-Administered PTSD Scale for DSM-IV) PTSD scale in the form of clinical interview for DSM-IV

In the authors' opinion, side effects occurring after taking methylenedioxymethamphetamine slightly differ from those observed after taking SSRIs. When comparing these therapies, it is important to keep in mind the interactions between paroxetine and sertraline taken for long periods with other medications. Substance addiction is a common problem in people struggling with post-traumatic stress disorder. Taking into account the recommendations on avoiding alcohol consumption throughout the course of treatment with SSRI drugs, this may prove to be another therapeutic difficulty in the treatment of patients struggling with post-traumatic stress disorder.

Currently ongoing research and extended access programs

The clinical trials currently conducted by MAPS, which began in 2018 in the United States, Canada and Israel, are in the third phase of clinical trials [38]. In May 2020, MAPS reported the results of one of two conducted phase 3 studies [39]. suggest that clinical trials on additional participants will not be necessary when the second necessary study is completed. This will allow access to a new form of treatment for patients suffering from post-traumatic stress disorder in the United States, probably as early as 2022.

European phase 2 studies are supposed to start in 2020 in the Netherlands, the Czech Republic, Norway, Portugal, and the United Kingdom [40].

In 2019, the Israeli Ministry of Health approved the use of MDMA-assisted psychotherapy in the treatment of PTSD in four centers, which will allow 50 patients to access treatment, while in 2020 the FDA authorized MAPS to implement an extended program of access to this type of therapy in the United States, which will allow another 50 patients to use it. These people will bear the costs of treatment themselves [41].

Discussion

There has been a growing interest in various treatment options that would allow for a more effective reduction of post-traumatic stress disorder symptoms. Therefore, MDMA is not the only substance whose effects are considered in the context of facilitating the ongoing therapeutic process. An example of other studies may be intranasal administration of oxytocin [42]. Furthermore, a pilot study using this substance as an adjunct to prolonged exposure psychotherapy has been conducted recently [43].

The studies conducted so far were carried out on small sample of respondents. Some authors also raise the issue of the variables like gender or age and oxytocin receptor gene polymorphism, which seem to be associated with therapeutic effects [44, 45]. Further work on similar studies may provide new therapeutic options significantly improving the functioning of patients with PTSD. It is important to point out that if MDMA-assisted therapy will be approved, it will be available for treatment-resistant patients, not for everyone who suffers from PTSD. These patients are not able to effectively confront their emotions related to traumatic memories, also due to problems with building a sufficiently strong therapeutic bond and administration of MDMA reduce these problems.

Moreover, in the beginning, the possibility of using this therapy may be limited due to the insufficient number of psychotherapists who would be qualified to conduct this therapy.

Another point to keep in mind is the possibility of limited reimbursement for this type of treatment. While the initial simulation of the cost-effectiveness of MDMA-assisted therapy [46] suggests being a cost-saving, if this therapy would not be reimbursed, as with recently registered esketamine for treatment-resistant depression, the cost of this treatment might be too expensive for many patients.

Conclusions

Methylenedioxymethamphetamine has a multidirectional effect that affects several areas of the brain and the neurotransmitter systems important from the point of view of a psychiatrist. The clinical trials conducted so far on the use of this substance in the treatment of PTSD have produced positive therapeutic results that are not associated with serious side effects that are burdensome for participants. No long-term side effects of the therapy were observed among the subjects, and no cases of addiction to this substance were reported after the end of the study. It is also worth emphasizing that although currently methylenedioxymethamphetamine is an illegal substance, its use does not seem to be associated with relatively high personal and social harmfulness [47]. In a study on the harmfulness of twenty widely used psychoactive substances, MDMA was ranked seventeenth. In the same publication, ethyl alcohol ranked first, tobacco ranked sixth, and benzodiazepines ranked tenth [47]. Although the irresponsible use of any type of stimulant can have serious health consequences, the data presented by the Multidisciplinary Association for Psychedelic Studies (MAPS) allow to look at MDMA from a completely different, new perspective.

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