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# Applications of MDMA in Modern Medicine- A Literature Review

# Zastosowania MDMA we współczesnej medycynie- przegląd literatury

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**Summary**

MDMA or 3,4- methylenedioxymethamphetamine is a psychoactive substance, exhibiting mild hallucinogenic properties, that became widely known as a recreational party drug. However, its ability in helping individuals access deeply rooted emotions has prompted significant interest in its potential applications within clinical practice. MDMA's mechanism of action involves increasing the release of serotonin, dopamine and oxytocin. This process enhances neuroplasticity, fosters empathy and aids in trauma processing and fear extinction. This study aims to explore the potential uses of MDMA in medicine, particularly in treating mental illnesses. The article was developed using data from the „PubMed" and „Google Scholar" databases, with particular emphasis on articles published after 2021. When combined with psychotherapy, MDMA offers significant therapeutic benefits, especially for patients resistant to conventional treatments. Existing research primarily highlights its effectiveness in managing post traumatic stress disorder (PTSD) and anxiety disorders, with emerging evidence suggesting potential benefits for conditions like depression and eating disorder. While

recreational use of MDMA poses risks, its use in a controlled environment demonstrates a favourable safety profile. Despite the highly promising results of MDMA- assisted therapy so far, additional clinical research is crucial to enable this drug to revolutionise future treatment methods.

**Keywords:** MDMA, psychiatry, psychotherapy, neurobiology, serotonin

**Streszczenie**

MDMA, czyli 3,4-metylenodioksymetamfetamina to substancja psychoaktywna o łagodnych właściwościach halucynogennych, która zdobyła popularność jako narkotyk używane rekreacyjnie na imprezach. Jednak jej zdolność do zwiększania dostępności do głęboko zakorzenionych emocji wzbudziła duże zainteresowanie jej potencjalnym zastosowaniem w praktyce klinicznej. Mechanizm działania MDMA opiera się na zwiększaniu uwalniania serotoniny, dopaminy i oksytocyny, co wpływa na neuroplastyczność, empatię, umożliwia łatwiejsze przetwarzanie traum i wygaszanie lęku. Celem niniejszego badania jest ocena zastosowań MDMA w medycynie, zwłaszcza w leczeniu schorzeń o podłożu psychicznym. Do opracowania artykułu użyto bazy danych „PubMed" i „Google Scholar", ze szczególnym uwzględnieniem artykułów opublikowanych po 2021 roku. W połączeniu z psychoterapią MDMA oferuje liczne korzyści terapeutyczne, zwłaszcza w przypadku pacjentów u których klasyczne metody nie przyniosły skutku. Dotychczasowe badania przede wszystkim podkreślają skuteczność MDMA w leczeniu zespołu stresu pourazowego (PTSD) i zaburzeń lękowych, a nowe dowody sugerują potencjalne korzyści w leczeniu depresji i zaburzeń odżywiania. Chociaż rekreacyjne użycie MDMA wiąże się z ryzykiem, jego zastosowanie w kontrolowanych warunkach wykazuje korzystny profil bezpieczeństwa. Pomimo obiecujących dotychczasowych wyników terapii wspomaganej MDMA, konieczne są dalsze badania kliniczne, aby ta substancja mogła zrewolucjonizować przyszłe metody leczenia.

**Keywords:** MDMA, psychiatria, psychoterapia, neurobiologia, serotonina

## Introduction

3,4-methylenedioxymethamphetamine (MDMA) was synthesised in 1912 by the German pharmaceutical company Merck with the intention of being a hemostatic drug, but all of the research performed on animal models has been destroyed during World War II. In the 1950s, U.S. Army started exploring MDMA's potential for mind control. However, they abandoned their efforts after discovering that its effects were similar to those of other stimulants. [1,2] In 1985, DEA classified MDMA as a Schedule 1 substance, due to its increased popularity in the party scene and potential of abuse. Over the past decade interest in its clinical potential has resurged.[3,4]

Classified as an entactogen, MDMA uniquely enhances self-acceptance and openess. Unlike classic psychedelics, such as LSD or psylocybin, MDMA does not provide psychedelic effects to the user. [5] Its primary mechanism involves increasing dopamine, oxytocin and serotonin levels, fostering emotional empathy and prosocial behaviour. These properties have driven growing interest in MDMA-assisted psychotherapy, particularly for conditions such as PTSD and anxiety. On the other hand, Evidence suggests that A range of medical review articles was examined to include both those supporting MDMA and those arguing against its effectiveness.MDMA can help patients access and process traumatic memories in a controlled, supportive setting. [6,7]

## Aim of the work

This reaserch paper explores potential applications of MDMA in the medical field, while also focusing on its molecular MoA potential side effects and effectiveness. A range of medical review articles was examined to include both those supporting MDMA and those arguing against its effectiveness.

## Methods

To compile this article, a total of 40 publications available in the PubMed and Google Scholar databases were used. To identify the most relevant sources, tho following combination of keywords was used: MDMA, 3,4-methylenedioxymethamphetamine, PTSD, anxiety, psychotherapy, psychiatry, psychedelics. To fully understand the topic, articles published between 2011 and 2024 were reviewed, with emphasis on those no older than three years. Our

focus was primarily on full- text review articles, meta-analyses, clinical trials and case studies that explored topics relevant to our subject of investigation.

## Literature review results

### Mechanism of action - MDMA

MDMA is as amphetamine-like substance that shares chemical similarities with 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDE) and methamphetamine. [8]

MDMA is rapidly absorbed after oral administration, reaching maximal concentration in approximately 2 hours. It exhibits nonlinear pharmacokinetics, meaning that higher doses lead to disproportionately increased systemic exposure. It is mostly metabolised in the liver via cytochrome P450 enzymes (especially CYP2D6), resulting in active metabolites such as MDA and hydroxylated compounds. These metabolites contribute to MDMA's pharmacological effects and are eventually excreted in urine. [9]

Euphoric and prosocial effects of this psychoactive drug primarily arise from its action on monoaminergic neurotransmitters, including serotonin (5-HT), dopamine (DA), and norepinephrine (NE). MDMA acts primarily by reversing serotonin transport through the serotonin transporter (SERT), leading to significant extracellular 5-HT accumulation in key brain regions such as the prefrontal cortex, hippocampus, and striatum. It affects 5-HT2A receptors, which promote cognitive flexibility and emotional responsiveness, and 5-HT1A receptors, involved in mood regulation and anxiety reduction.The interaction of these receptor systems result in a synergistic effect and increase positive feelings, emotional lability and psychological adaptability.[10] The dopaminergic activity of MDMA is particularly prominent in brain regions such as the nucleus accumbens, ventral tegmental area, and prefrontal cortex. These areas are involved in motivation, reward and executive function. However MDMA is more effective at releasing 5-HT than DA, as it exhibits a greater affinity for SERT compared to DAT (dopamine transporter). [11]

### PTSD

Post traumatic stress disorder is characterised by persistent feeling of unexplainable fear and intrusive memories, which results from experiencing traumatic events. Selective serotonin reuptake inhibitors (SSRIs) and trauma-focused psychotherapies are the pillars of conventional

PTSD treatment. However, a significant amount of patients is not able to achieve remissions. One of the newest prospects is MDMA, which has shown great potential as a supportive tool in therapy as it assists patients in trauma processing and decreases the severity of symptoms. By influencing serotonin receptors, especially 5-HT2A and 5-HT1A, MDMA promotes neuroplasticity changes by reducing amygdala's activity . This particular region is often linked with intense fear responses in patients with PTSD. [12]

In studies on MDMA, changes in c-fos expression have been connected to how the drug affects the way fear-related memories are processed. Increased levels of c-fos mRNA serve as a sign of brain activity. Changes in the expression of c-fos in the amygdala and medial prefrontal cortex (mPFC) has been linked to a decrease in conditioned freezing behaviour, which is a sign of fear response. Moreover, lower levels of BDNF in these brain areas are connected to a higher risk of developing PTSD. Additionally, low BDNF levels are associated with reduced success rate in exposure-based therapies. This emphasises the critical role of BDNF in recovery and highlights its potential as a key focus for therapeutic interventions. Experimental findings in rodents demonstrated that MDMA selectively increased BDNF expression in the amygdala, but this effect was dependent on concurrent extinction training sessions. No significant changes in BDNF levels were observed in the amygdala when MDMA was administered without subsequent extinction training, nor were effects noted in the mPFC under similar conditions. This suggests that MDMA's ability to facilitate fear extinction relies on the interaction between pharmacological action and behavioral interventions. [13,14]

In a phase 3 randomised, double-blind, placebo-controlled trial, researchers studied the safety and effectiveness of MDMA- assisted therapy (MDMA-AT) in patients with underlying PTSD. It consisted of 104 participants and its results were assessed with Clinician- Administered PTSD Scale for DSM-5 (CAPS-5) and the Sheehan Disability Scale (SDS). A considerable decrease in PTSD symptom severity was observed, as measured in CAPS-5 scores. Moreover, 71.2% of participants no longer met the criteria for PTSD, in comparison to 47.6% in the placebo group. [15] MDMA-assisted psychotherapy shows great potential, especially for cases that do not respond to conventional treatments. However, it also comes with significant challenges and potential risks. Treatment outcomes can vary depending on factors, such as the complexity of a person's trauma, their unique brain chemistry, and whether they have other underlying health conditions. Patients with severe anxiety or depressive symptoms often benefit the most from MDMA- assisted therapy. Those with complex PTSD or other psychiatric disorder may require

additional therapeutic support. Moreover, neurobiological differences, such as variations in serotonin transporter gene polymorphisms may play an important role in efficiency of the treatment. [16]

In July of 2023 Australia became the first country to approve MDMA therapy for PTSD and treatment-resistant depression. It is a milestone for psychedelics use in modern therapy. However, it still possesses challenges related to its high costs and limited accessibility. [17]

**PTSD in comorbidity with ED**

Eating disorders (ED) and PTSD share a numer of risk factors, such as sexual abuse, childhood maltreatment and emotional dysregulation. Around 24% of ED cases present with PTSD symptoms. What is more, underlying trauma in ED patients often manifests with earlier onset and more severe symptoms.[18] It is thought that binge eating, food restriction and purging, which are typical symptoms of an eating disorder can be used to manage intrusive memories in PTSD. Treatment of ED in PTSD populations is accompanied by higher dropout rates from therapy, as patients are distrusting. These individuals are also at a higher risk of relapsing. A promising solution is to combine trauma-informed care and ED interventions. [19] MDMA—assisted psychotherapy remains experimental tool, yet it shows great potential. It already proved to be effective in patients with PTSD and in combination with Cognitive Behavioral Conjoint Therapy (CBCT) used in therapy of PTSD couples. [20].

MDMA's effects in reducing ED symptoms with comorbid PTSD were assessed in a phase 3, double-blind, placebo-controlled trial, consisting of 90 participants. It consisted of three 8-hour sessions with a 4-week break. ED symptoms were evaluated at the beginning and end of the study, using the Eating Attitudes Test (EAT-26). PTSD symptoms were assessed using the Clinician-Administered PTSD Scale (CAPS-5). 15% of participants scored in the clinical range (EAT-26 $\geq$ 20) and 31.5% in the high-risk range ( EAT-26 $\geq$ 11), although they were not underweight. MDMA- assisted therapy significantly reduced EAT-26 scores in comparison to placebo-assisted therapy. The biggest improvement was shown in women with high baseline EAT-26 scores ($p = 0.0012$ for EAT-26 $\geq$ 11 and $p = 0.0478$ for EAT-26 $\geq$20).[21] However, the research is still in its early stages with challenges such as small sample sizes and limited data on long-term effects. It is crucial to further investigate safety concerns for ED patients. Low weight increases the risk of electrolyte imbalance or heart conditions. Moreover, MDMA's

activity on serotonin receptors may interact with antidepressants or other medications causing adverse effects. We already know, that in combination with MAOIs it can lead to serotonin toxicity. [22]

**Anxiety**

Anxiety is both a psychological and physiological condition. It manifests in emotional and behavioural responses to actual or perceived threats. Anxiety disorder is one of the biggest challenges in psychiatry, as it affects approximately 14.7% of the population. [23] MDMA works by enhancing the activity of serotonin, dopamine and norepinephrine neurotransmitters, which are essential for stress management and mood regulation. It has the biggest impact on serotonin release, by activating 5-HT2A receptors, responsible for emotional resilience and the feeling of safety. [24] What is more, MDMA presents entactogenic effects, increasing feelings of love, joy , and emotional connection to others. This emotional enhancement is complemented by rapid anxiolytic effects observed in both animal and human studies. [25]

In pooled data from six studies, MDMA increased empathy for both positive and negative emotions, with a stronger effect on positive stimuli. Participants under the influence of MDMA reported heightened concern for others and greater emotional sensitivity compared to placebo conditions. [26] MDMA also triggers oxytocin release, which enhances trust and social bonding. It is particularly beneficial in addressing interpersonal difficulties characteristic of anxiety disorders like Social Anxiety Disorder (SAD). [24] Patients with SAD often relive moments of embarrassment and humiliation from the past. In a randomized, double-blind, placebo-controlled pilot study conducted on autistic adults with Social Anxiety Disorder (SAD), participants in the MDMA group showed significant reductions in social anxiety, as measured by the Liebowitz Social Anxiety Scale (LSAS), compared to those in the placebo group. These improvements persisted at a six-month follow-up. Participants reported enhanced confidence in social interactions, reduced avoidance behaviors, and improved relationships, highlighting durable benefits beyond the active treatment phase. [27]

**Depression**

Major depressive disorder (MDD) is a complex condition, characterised by longterm decrease in mood, anhedonia and recurring suicidal thoughts. [28] Antidepressant-like qualities of

MDMA have been previously investigated in rats that exhibited depression-like behaviour. MDMA was given at 5mg/kg and 10mg/kg with evaluations taking place after both one-time and repeated doses. In order to distinguish between antidepressant-like qualities of MDMA and its stimulant effects a forced swimming test (FST) was conducted. It assessed changes in behaviour, as well as locomotor activity. Single dose administration of MDMA resulted in substantial decrease in immobility in FST, especially at the higher dosage. Conversely, continuous administration of the drug reduced beneficial effects of the single dose administration and lead to increased depressive activity. Findings reveal that MDMA could serve as an acute treatment for depression. Nevertheless further investigation is required to estimate long-term impact of MDMA therapy. [29]

Current MDMA research in humans has primarily focused on PTSD treatment. However, there is limited data available regarding its therapeutic use in major depressive disorder. The study by Mithoefer, Michael C et al. has investigated the effects of MDMA-assisted psychotherapy (MDMA-AT) in individuals suffering from PTSD, in some cases followed by comorbid depression. In this research, 30, 75 and 125 mg of MDMA has been administered in two 8-hours sessions, for the duration of 12 months. Depression symptoms were assessed using the Beck Depression Inventory-II (BDI-II), which showcased a significant decrease in severity of depression and overall improved psychological well-being. Research indicated that higher doses of MDMA (75 mg and 125 mg) were associated with enhanced therapeutic effects compared the low dosage group (30 mg). The benefits of MDMA-AT persisted for 12 months after the last session for the majority of participants. [30]

**Adverse effects of MDMA**

Although MDMA is a highly promising drug in treatment of psychiatric disorders, there are multiple concerns regarding its toxicity. [31] The most common side effects are headaches, fatigue, anxiety, jaw-clenching, uncontrolled eye movements and nausea. [bruhwhy] Moreover, studies show that chronic use of MDMA is linked to impairment of declarative and working memory and various executive functions. This negative effect on memory is even more prominent in combination with other stimulants. [32]

MDMA metabolites, such as α-methyldopamine (α-MeDA) and 3,4-dihydroxymethamphetamine (HHMA) are related to increased neurotoxicity of the drug. Their

ability to produce reactive oxygen species (ROS) and nitrogen species (RNS) leads to inhibition of mitochondrial complex I and disruption of energy metabolism, resulting in neuronal cell death.[33,34] Another key neuroinflammatory factor is activation of astroglial and microglial cells, that results in elevated cytokines and nitric oxide levels. Adenosine receptor agonists/ antagonists are thought to be able to counteract those negative effects of MDMA. Adenosine acts as a anti-inflamamatory agent, by regulating dopamine and glutamate pathways, reducing cytokine production and glial cell activation.[35] Excitotoxicity is another issue, caused by an excessive release of neurotransmitters (serotonin and dopamine). Individual studies indicate that the simultaneous administration of antioxidants like dextrorphan, could have protective effects.[34]

**MDMA adverse effects outside controlled environments**

Since its rise to fame in the 80', MDMA has been consistently used for recreational purposes in the party scene, appealing mostly to younger audiences. Its popularity can be attributed to its low addictive profile and psychedelic effect that promotes feelings of closeness and euphoria.[36] In uncontrolled environment usage of MDMA can lead to various adverse effects, including death.

The main mortality factors are hyperthermia, dehydration and hyponatremia, further induced by frequent co-use of alcohol in party settings. Increased body temperature is associated with the action of serotonin and dopamine in the hypothalamic region. It can lead to increased oxidative stress and mitochondrial dysfunction, resulting in multiple organ failure. Additionally, increased consumption of isotonic drinks as a method to regulate body temperature can result in hyponatremia. It can manifest as a headache, loss of consciousness and even cerebral herniation.[37]

Prolonged MDMA use is also linked to heightened cardiotoxic effects. Release of monoamines (dopamine, norepinephrine) leads to increased heart rate and blood pressure, while activation of alpha-adrenergic receptors promotes coronary vasospasm and ischemia. Taking into account factors mentioned above, users can develop life-threatening arrhythmias. [38]

**Co-use with classic psychedelics**

Based on current scientific evidence, classic psychedelics have the potential to revolutionise modern therapy methods. LSD and psylocybin induce unique altered states that enhance a sense

of connection to others, promote emotional acceptance and provide deep self-insights. It shows great promise in anxiety, depression and PTSD treatment, though it can lead to challenging psychological experiences, like fear, paranoia or grief. [39] MDMA is a serotonergic entactogen, which promotes emotions of love and gratitude and can acts as a buffer against negative emotional states.

Study on the co-use of MDMA with classic psychedelics involved 698 participants, who were planning to use classic psychedelics, were grouped based on the MDMA dosage (none, low, medium-high). Results were assessed with Challenging Experience Questionnaire and Mystical Experience Questionnaire and subjective ratings for pleasurable experiences. The study has proven that low-dose of MDMA with psylocybin/LSD significantly reduced negative experiences, including fear and grief and enhanced positive ones. However, this effect did not occur with medium-high doses. [40]

**Conclusions:**

The use of MDMA holds great promise as a novel option for treating mental health disorders , particularly for those who have not responded well to conventional treatments. Its unique pharmacological properties, which enhance emotional processing, neuroplasticity and empathy position it as a valuable supplement to psychotherapy. Trials in clinical setting have revealed a notable improvement in individuals suffering from PTSD and anxiety, with potential implications for treating eating disorders and depression. However, in order to fully grasp its effectiveness as a standardised treatment, more extensive studies with standardised protocols and bigger experimental groups are advised. What is more, future research should investigate MDMA' effects in other applications and in comparison with variety of modern drugs. Nevertheless, MDMA remains an illegal substance, which complicates its testing and research.

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