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3,4-Methylenedioxyamphetamine: From Dangerous Party Drug to Potential Therapeutic Agent

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ABSTRACT

Introduction and aim of the study: 3,4-methylenedioxymethamphetamine (MDMA) is a stimulant drug with widespread consumption. It is used mainly in recreational settings, due to its ability to induce various pleasurable, mood-enhancing effects. Prolonged and excessive MDMA misuse can lead to multiple negative outcomes ranging from cognitive dysfunction or emotional dysregulation to severe life-threatening consequences such as hyperthermia. Despite its harmful potential, MDMA presents promising therapeutic applications in MDMA-Assisted Therapy. In this study we aim to review both the dangers and potential psychiatric applications of MDMA.

Materials and methods: A literature search was conducted using databases such as PubMed and Google Scholar. The review focused on peer-reviewed articles and international reports regarding the use of MDMA, both recreational and in the treatment of various psychiatric conditions.

Conclusions: While MDMA has traditionally been associated mainly with recreational use and addiction, research suggests it has the potential to become a valuable therapeutic adjunct in treating such psychiatric conditions as PTSD, alcohol dependence, depression and anxiety. Furthermore, it could be beneficial in the athletic populations.

However, existing studies are limited by small sample sizes, highlighting the need for further large-scale research to confirm these findings.

Keywords: MDMA, MDMA-Assisted Therapy, PTSD, alcohol dependence, depression, anxiety, mental health of athletic populations

1. Introduction

3,4-methylenedioxymethamphetamine (MDMA, also referred to as “ecstasy,” “E,” “X,” or “Molly”) is an amphetamine-like recreational drug belonging to a wider category of drugs: stimulants.

Its consumption is widespread, as according to estimates from the United Nations Office on Drugs and Crime in 2023 the annual prevalence of ecstasy use in the global population aged 15–64 was approximately 21.5 million individuals [1]. It is especially common amongst ravers and is, therefore, often described as a “club drug” [2]. Despite its reputation as a recreational substance, the dual nature of MDMA, characterized by both significant neurotoxic risks and potential clinical benefits, has sparked renewed interest in the scientific community. This article aims to give a brief review of its effects on mood, dangers connected to excessive usage, and its emerging therapeutic properties.

2. Historical Context

The historical trajectory of MDMA is unique, spanning from its initial laboratory synthesis to its emergence as a controversial street drug, and finally returning to its status as a potentially breakthrough medicine. Its origins date back far before it reached the public spotlight, extending to around 1912 when it was first synthesized by the German pharmaceutical company Merck, which intended to create a new blood-clotting medication. MDMA was synthesized as an intermediate chemical compound in the process of synthesizing a haemostatic substance called hydrastinine [3]. For decades, the compound remained largely forgotten in pharmacological archives; indeed, prior to 1953, MDMA was mentioned only twice in the scientific literature, once more as a byproduct of a chemical reaction. In 1953, the substance resurfaced when it was tested, among other chemicals, on mice by the Army Chemical Center to evaluate its potential as a chemical weapon. A significant turning point occurred in the 1970s, when the chemist Alexander Shulgin, who is sometimes mistakenly recognized as the creator of MDMA, managed to resynthesize the drug. Subsequently, in 1978, the first human study of MDMA was published in an article by Shulgin and Nichols. In their work, they describe the effects of MDMA as “an easily controlled altered state of consciousness with emotional and sensual overtones” [4]. Shulgin then introduced the substance to his colleagues and the psychotherapeutic community, and throughout the late 1970s and 1980s, MDMA was utilized by hundreds of therapists in the United States to facilitate their clinical work.

The substance, which among therapists gained the name “Adam”, meaning “the condition of primal innocence and unity with all life,” as described in the Bible’s account of the Garden of Eden [5], is said to have reached as many as four thousand practitioners. However, the substance soon transcended its clinical setting and gained massive popularity within the nightlife scene of the 1980s. This rapid rise in recreational use caught the attention of Lloyd Bentsen, a Texas Democratic Senator, who pressured the Drug Enforcement Administration (DEA) to criminalize MDMA. When the DEA announced its intention to classify MDMA as a Schedule I substance, meaning that it is prohibited for every application, has no recognized medical use, and cannot be prescribed by a physician, a group of psychiatrists and psychotherapists opposed the move, initiating a dispute within the scientific community [6].

Eventually, after extensive discussion and mainly due to growing concerns over its neurotoxic potential weighed against mainly anecdotal evidence of therapeutic properties, the DEA finally classified MDMA as a Schedule I substance on March 23, 1988 [6]. This decision effectively halted most clinical research for nearly two decades, creating a long hiatus in our understanding of its therapeutic benefits until the recent “psychedelic renaissance” of the 21st century.

3. Recreational Use

MDMA is a drug primarily consumed in the form of variously shaped, often colourful tablets or capsules, however it can also be administered intravenously or insufflated [7]. MDMA intake is said to produce various pleasurable effects which are the primary factors driving its consumption. The onset of these subjective manifestations typically occurs between 30 and 60 minutes post-ingestion, with the experience reaching its peak after 75 to 120 minutes and maintaining a sustained plateau for approximately 3.5 hours [8]. The effects that received the highest ratings in an internet survey conducted in the UK are: “changed outlook on life” “understanding of self” “improved relationships”, “increased sociability”, “improved psychological functioning” and “healthiness”. Users also report increased enjoyment of music and/or dancing, enhancement of sex, a greater sense of closeness to nature, and the experience of an altered state of consciousness [9][10].

4. Neurobiological Mechanisms

The neurochemical mechanisms underlying MDMA’s acute effect on human mood are relatively well established. MDMA acts primarily by binding to serotonin (SERTs), dopamine (DATs) and norepinephrine transporters (NETs), where it blocks the reuptake and stimulates the release of serotonin, dopamine and norepinephrine respectively [11][12].

MDMA has also been shown to elevate oxytocin levels, potentially facilitating the strengthening of social bonds [13][14].

Furthermore, functional magnetic resonance imaging (fMRI) studies propose that MDMA consumption decreases amygdala activity at the same time increasing the ventromedial prefrontal activity, which could positively influence subjects’ emotional regulation as well as fear and avoidance behaviour [10][11].

In addition, MDMA appears to influence interoception, the perception and interpretation of bodily signals, which is often altered in depression and anxiety disorders. fMRI studies have demonstrated that individuals with impaired interoception exhibit changes in brain circuitry that correlate with brain areas impacted by MDMA, notably the insula. These neurobiological mechanisms may partly explain the substances’ capacity to potentiate the effects of psychotherapy [17-21].

5. Risks Connected to MDMA Consumption

Some studies have shown that chronic MDMA usage poses certain risks, such as behavioural changes and addiction. To understand the long-lasting behavioural effects that prolonged MDMA consumption may produce, it is first necessary to consider its neurotoxicity. As multiple studies have shown, high doses of MDMA lead to various changes in the brain, such as long-lasting depletion and reduced reuptake of serotonin, reduction in SERT binding sites and lowered activity of tryptophan hydroxylase, an enzyme involved in serotonin production [11]. Moreover, histological studies of brain tissue of rats and monkeys treated with MDMA revealed reduced density of serotonergic axons, suggesting that the consumption of the drug leads to axonal degeneration [11,22]. However, different experiments suggest that the neurons may not be damaged, but their activity is changed by reduction of expression of SERT and tryptophan hydroxylase genes [23,24]. These both findings, referred to as the neurodegeneration and downregulation hypothesis of MDMA neurotoxicity, point to the fact that MDMA is a serotonergic neurotoxin [24].

Parrot [25] and other researchers [26-28] propose that a causal relationship exists between changes of cognition and mood in ecstasy users and the previously described serotonergic dysregulation. The cognitive changes mainly include prospective, retrospective and working memory impairment as well as disturbances in complex cognitive processes. The mood disturbances in MDMA users encompass increased anxiety levels, feeling of depression, sleep and appetite disturbance and aggravation of aggression [29].

It is important to notice that, despite the common belief that MDMA consumption does not pose risk of addiction, that is simply not true. Some studies even suggest that MDMA tolerance can develop even within single use and regular users describe the need to increase the dose as the positive effects are not that well pronounced [30,31]. What is more, users reported a myriad of symptoms that are related to drug dependence, such as “significant time spent using and/or recovering from ecstasy use”, “difficulty reducing or stopping ecstasy use despite the

recognition of drug-related problems”, “reduced time spent in other activities”, “higher levels of risky behaviour”, and “withdrawal symptoms accompanied by drug craving” [32].

The life-threatening complication associated with MDMA use is hyperpyrexia, which can result in fatal outcomes such as rhabdomyolysis or disseminated intravascular coagulation [33].

Although this condition most frequently occurs in recreational settings—typically characterized by elevated ambient temperature, overcrowding, and prolonged physical exertion—several cases have been documented in which hyperthermia developed despite the absence of these contributing environmental factors [34]. Patel suggests that genetic predisposition may contribute to the development of MDMA-induced hyperpyrexia. The metabolism of MDMA is carried out primarily by CYP2D6, a polymorphically expressed cytochrome-P450 isoenzyme [35], indicating that individuals with reduced CYP2D6 activity may demonstrate higher susceptibility to hyperthermic reactions.

It is worth mentioning that out of total 183 MDMA induced hyperthermia cases reported in the literature, none has occurred in clinical settings [36].

It is important to underline that however abovementioned complications are usually connected to excessive and prolonged recreational use, MDMA-Assisted Therapy is not entirely free of adverse effects. The somatic adverse effects connected to MDMA-Assisted Therapy are usually mild and the most commonly reported include muscle tightness, nausea, and decreased appetite. Psychiatric adverse effects have also been reported, such as suicidal ideation, insomnia and anxiety. However, it is worth mentioning that in the study that reported such effects, the majority of participants had preexisting suicidal ideation [37].

Another subject worth keeping in mind is that a clear distinction must be made when considering safety of MDMA-Assisted Therapy between “Ecstasy”, usually consumed for recreational purposes on the streets and pure MDMA used in clinical settings. Street Ecstasy is often contaminated with other substances such as amphetamines, fentanyl or cocaine, significantly changing its safety profile [38].

6. Therapeutic Potential:

MDMA-Assisted Therapy (MDMA-AT) is not an entirely modern concept, as Leo Zeff, an American psychotherapist has treated multiple patients with MDMA-Assisted Therapy until 1985, when due to the high prevalence of recreational MDMA use it was declared no longer legal [38].

Nowadays however we are witnessing a renaissance of usage of psychoactive substances as a way to treat psychiatric conditions. Multiple trials emerge with the aim of studying the therapeutic potential of MDMA-Assisted Therapy for conditions such as PTSD, depression, anxiety and even substance abuse.

6.1 MDMA-Assisted Therapy Structure

MDMA-Assisted Therapy (MDMA-AT) comprises three types of sessions: preparatory, MDMA and integration. The preparatory sessions are usually three 90-minute-long psychotherapy sessions with the aim of building therapeutic alliance with the patient and educating them.

After preparatory sessions MDMA sessions take place. During one course of treatment the patient is subject to two to three MDMA sessions, 6-8 hours long, about one month apart. During one MDMA session two doses of MDMA are administered. First dose of 75-125 mg and the second, supplementary, dose of half of the initial dose after 90-120 minutes. In these sessions therapists aim to guide the patient to focus inward, attention is centred on what is happening in the patient's body, while fostering a sense of safety.

Each and every one of MDMA sessions is followed by 3 integration sessions, the first one taking place the morning after the MDMA session. The second and third one follow approximately one week apart. The purpose of these sessions is the exploration of the insights, thoughts and emotions that emerged during the substance use and getting a deeper understanding of them [38,39].

6.2 MDMA-AT and Post Traumatic Stress Disorder

Post Traumatic Stress Disorder (PTSD) is a debilitating psychiatric disorder that can develop after exposure to severe stress or traumatic events, characterised by symptoms such as intrusive memories, emotional numbing,

hyperarousal and avoidance behaviours, that impair one's ability to function properly on a daily basis [35]. It affects around 1-3% of the European population as well as around 5% of the US population each year. It has been reported that in 2020 about 13 million Americans experienced PTSD [39,41].

The current gold standard for treating PTSD, trauma-focused psychotherapy, is often insufficient and many patients decide to discontinue the treatment [42]. Drugs such as paroxetine and sertraline have been approved for treating PTSD symptoms, however it is ineffective in about 35-47% of individuals [43]. This shows that the need for a more effective treatment is imperative.

MDMA-AT is gaining attention as a potential remedy for the lack of effective PTSD treatment. In a 2024 article Wolfgang collected data from eight randomised placebo-controlled clinical trials, two of which were phase 3 trials, encompassing nearly 300 participants with PTSD diagnosis, resistant to previous therapies. Four weeks after the last MDMA session 67-71% of participants of both phase 3 trials lost the diagnosis of PTSD after MDMA-AT as compared to 32-48% after placebo-assisted therapy. Phase 2 studies show continued improvement in diagnostic outcomes at the 1-year follow-up and remain stable with 74% of participants no longer meeting PTSD diagnostic criteria almost four years later [38].

6.3 MDMA-AT and Alcohol

Alcohol use disorders (AUDs) are one of the most common mental disorders globally. The World Health Organization (WHO) reported that in 2019, an estimated 400 million people (7% of the global population aged 15 and older) lived with alcohol use disorders [44].

Current therapeutic options used for the treatment of alcohol use disorders remain insufficiently effective, which has prompted a renewed scientific interest in psychedelic-assisted psychotherapy [45].

In 2012, a meta-analysis of six randomized controlled trials conducted in the 1950s and 1960s evaluated the use of LSD in the treatment of alcohol use disorder. The study demonstrated generally favourable outcomes: 59% of participants who received LSD showed significant clinical improvement, compared with 38% in the control groups [46].

The theory proposed to explain these effects emphasizes the role of profound, often spiritual experiences, which may facilitate shifts in motivation, self-perception, and behavioural patterns helping to sustain sobriety. Although MDMA does not share an identical pharmacological profile with classic psychedelic drugs, it exhibits several overlapping mechanisms, particularly in its modulation of serotonergic and emotional-processing pathways, thereby suggesting potential therapeutic effects for alcohol misuse [47].

Recently, the first MDMA-assisted study for treating patients with alcohol use disorder was conducted, The Bristol Imperial MDMA in Alcoholism Study. This open-label trial enrolled fourteen individuals with AUD who had completed alcohol detoxification and subsequently participated in an eight-week course of psychotherapy. Each patient underwent two sessions in which they received 187.5mg of MDMA each session. Outcomes such as mental well-being, psychosocial functioning and drinking behaviour, measured in units of alcohol consumption per week, were assessed over nine months after the alcohol detoxification.

At the nine-month follow-up end point, 11 of the 14 eligible participants consumed less than 14 units of alcohol per week, including nine who achieved complete abstinence, whereas three participants relapsed to drinking more than 14 units per week. On average, weekly alcohol consumption decreased from 130.6 units, in the month prior to detoxification, to 18.7 units per week [48].

6.4 MDMA-AT and Depression

Major Depressive Disorder (MDD) is a common psychiatric disorder, affecting approximately 7,2% European Union citizens [44]. The disease can be debilitating, and the available treatment options are insufficient. A small proof-of-principle study has been conducted in 2025 by Kvam with the aim of investigating the potential therapeutic role of MDMA-AT in treating MDD. It included 12 participants, 7 of which female and 5 male, with the diagnosis of moderate to severe MDD, who received the MDMA, assisted with psychotherapy before, during and after administration, twice. The study assessed MDD symptoms with a usage of Montgomery–Asberg Depression Rating Scale (MADRS), a standard scale used in determining the severity of depression symptoms. The mean baseline MADRS for all participants was 29.6. At the primary outcome point, around two months after

the second MDMA session, the mean MADRS reduction was -19,3 as the mean MADRS reached 9.7. The change was statistically significant with $p < 0.001$ [50].

6.5 MDMA-AT and Anxiety

MDMA-AT could also represent a promising approach in reducing anxiety. A small double-blind randomized study explored the therapeutic potential of MDMA-AT for adults suffering from anxiety related to life-threatening illnesses. The participants received two MDMA-AT sessions. The outcome of the sessions was assessed using State-Trait Anxiety Inventory (STAI) At the primary endpoint, participants receiving MDMA showed a decrease in STAI-Trait scores of -23.5, which is greater reduction in anxiety as compared to the -8.8 reached by the placebo group. However, the results don't show statistical significance with $p = 0.56$ [51].

Another small double-blind randomized study investigated the reduction of social anxiety in autistic adults after MDMA-AT. In this study the participants also received two MDMA-AT sessions, and the results were measured using Leibowitz Social Anxiety Scale (LSAS). The MDMA group has shown significantly greater improvements in LSAS as compared to placebo group at both, the primary endpoint one month after the second MDMA session ($p = 0.037$) and the 6-month-follow-up ($p = 0.036$) [52].

7. MDMA use among athletic populations and its potential to improve mental health in athletes

MDMA has been listed in the S6 Section (Stimulants) on the List of Prohibited Substances and Methods issued by the World Anti-Doping Agency (WADA) and is a genuine concern for the athletic world as in the study conducted by Dunn et al. 25.9% of surveyed athletes said "that they had been offered or had the opportunity to use" it, and 3.7% reported recent use [53, 54]. Its role in the elite sports world is not that evident, as, unlike other substances frequently abused by athletes to enhance performance, MDMA can actually decrease it by negatively affecting thermoregulation and muscle functions [25]. What is more, MDMA is said to increase the risk of hyponatremia in humans, which may negatively impact the athletes' endurance, and as a group, psychedelic substances have been shown to cause biphasic effects on locomotion in rats [55, 56]. Thus, MDMA in the athletic populations is rather not consumed with the primary goal of increasing performance. Although research on the topic is limited, it can be speculated that an athlete's motivation to use psychedelics is primarily driven by their ability to positively affect mood between competitions due to their potential to reduce anxiety, enhance resilience, and improve social dynamics [57].

As shown in the studies above, MDMA and MDMA-AT exhibit long-lasting therapeutic potential, combined with a favorable safety profile, in various psychiatric conditions. Research suggests that due to significant stressors, such as high demand for performance, conflicts in competitions, overtraining, injuries, and early retirement the prevalence of psychiatric conditions among both amateur and professional high-performance athletes may be greater than in the general population [58-61]. Because of self-imposed pressure to show mental resilience, athletes might avoid reporting health issues, refuse professional help, or not follow treatment plans. Moreover, athletes may also avoid pharmacological treatment of these conditions due to the medications' effects on their performance and potential adverse effects [62, 63]. Taking the variables mentioned above into consideration, psychedelic therapy, including MDMA-AT, might be worth exploring for treating psychiatric conditions in athletes.

Psychedelic therapy and MDMA-AT offer a few potential benefits over conventional medications in the athletic populations. Primarily, psychedelic therapy features only a few sessions spaced over weeks to months, possibly granting long-term results. Secondly, these substances have a relatively short half-life of about a few hours. These properties reduce the risk of them and their potential adverse reactions affecting athletic performance during competition and training [64, 65]. As the data is limited, further research into the topic of psychedelic therapy and MDMA-AT, and the mental health of athletic populations, is recommended.

8. Conclusion

MDMA remains a highly controversial substance. Belonging to the group of stimulants, known mainly for their recreational misuse and abuse, it also shows clinical promises.

The dangers connected to excessive and prolonged ecstasy consumption, such as negative effects on mood, cognition and emotional regulation are well documented. In conjunction with the widespreadness of the substance it can present significant public health concern. However, current research suggests that the therapeutic potential of MDMA should be evaluated separately from its recreational usage, as emerging studies suggest that MDMA-Assisted Therapy could be a potent agent in the arsenal of methods used to treat psychiatric conditions such as

PTSD, alcoholism, depression or anxiety. Furthermore, it could be beneficial in the athletic populations. Although MDMA-AT has shown particularly strong results in the treatment of PTSD, with clinical trials reaching phase 3, for other conditions the amount of data is still limited, but promising. Regarding the potential adverse effects connected to the usage of MDMA in therapy, it is important to emphasize that the majority of severe psychological and somatic adverse effects described in literature occur in nonclinical settings, while MDMA-AT follows a strict protocol which aims to reduce the risk of such dangers occurring.

Overall, current evidence indicates that MDMA has the potential to evolve from a substance that is mainly associated with recreational misuse into a valuable additive in psychiatric treatment, provided that its administration remains restricted to rigorously controlled therapeutic settings.

It is important to remember that however in the studies we cited, the preliminary findings indicate positive and encouraging outcomes in the treatment of alcohol use disorder, major depressive disorder, and anxiety-related symptoms, each study was limited by a notably small sample therefore they remain insufficient to support definitive conclusions. Across these diagnostic categories, rigorously designed trials with larger and more diverse cohorts are essential to confirm these early results in order to determine the safety profile and clinical benefit of MDMA-Assisted Therapy.

9. Disclosure

Author's contribution

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