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From the party to the therapy – MDMA as an alternative for the existing methods of Post-traumatic Stress Disorder treatment

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Abstract

Introduction: Post-traumatic Stress Disorder (PTSD) is a mental illness caused by exposure to a traumatic event. The current treatment includes trauma-focused psychotherapy along with selective serotonin reuptake inhibitors (SSRI). It is estimated that for about 40-60% of patients it does not bring the desired improvement, which prompted scientists to look for new methods of pharmacotherapy. The most promising compound is MDMA.

Material and methods: The purpose of this paper is to review publications from years 2020-2022 available on the PubMed platform about using MDMA in PTSD treatment, using words: MDMA, PTSD, MDMA and PTSD.

Discussion: MDMA (3,4-methylenedioxymethamphetamine) is a psychoactive substance that increases brain levels of serotonin, dopamine and norepinephrine. Studies show that this treatment reduces symptoms of severe PTSD, comparing to placebo and current treatment. Patients reported improvement in terms of well-being, number of nightmares, sleep disorders, self-perception or interpersonal relationships. The positive effects of MDMA therapy were long-lasting. They persisted for 12 months after the end of treatment. According to research, MDMA reduces the symptoms of concomitant disorders, e.g. of eating disorders or by reducing alcohol consumption, without increasing the risk of abuse of other substances or MDMA itself. In addition, MDMA is believed to improve psychotherapy by allowing patients to revisit the traumatic event without negative symptoms. Side effects of therapy are less serious and occur less often than in the case of previously used SSRIs.

Conclusions: Abovementioned observations show that MDMA-assisted PTSD psychotherapy is a promising alternative to the existing methods and brings hope for patients with the most severe or treatment-resistant course.

Keywords: MDMA, N-Methyl-3,4-methylenedioxyamphetamine, MDMA-assisted psychotherapy, PTSD

Streszczenie

Wstęp: Zespół Stresu Pourazowego (PTSD) to zaburzenie psychiczne spowodowane narażeniem na traumatyczne wydarzenie. Aktualnie leczenie opiera się na psychoterapii skoncentrowanej na traumie w połączeniu z inhibitorami wychwytu zwrotnego serotoniny (SSRI). Szacuje się, że u około 40-60% pacjentów nie przynosi ono pożądanej poprawy stanu, co skłoniło naukowców do poszukiwania nowych metody farmakoterapii. Obecnie najbardziej obiecującym związkiem jest MDMA.

Materiał i metody: Celem tej pracy jest przegląd publikacji naukowych dostępnych na platformie PubMed na temat wykorzystania MDMA w terapii PTSD z lat 2020-2022, używając słów: MDMA, PTSD, MDMA and PTSD.

Dyskusja: MDMA (3,4-metylenodioksymetamfetamina) to związek psychoaktywny zwiększający poziom serotoniny, dopaminy i noradrenaliny w mózgu. Badania pokazują, że taki sposób leczenia zmniejsza objawy PTSD o ciężkim przebiegu w porównaniu z próbami placebo oraz dotychczasowym leczeniem. Pacjenci zgłaszali poprawę m.in. w zakresie samopoczucia, liczby koszmarów, zaburzeń snu, postrzegania siebie czy relacji międzyludzkich. Pozytywne efekty terapii MDMA były długotrwałe - utrzymywały się przez 12 miesięcy po zakończeniu leczenia. Według badań, MDMA wpływa na zmniejszenie objawów chorób często towarzyszących PTSD, tj. zmniejszenie spożycia alkoholu oraz objawów zaburzeń odżywiania przy jednoczesnym braku zwiększania ryzyka nadużywania innych substancji czy samego MDMA. Ponadto, uważa się, że MDMA usprawnia psychoterapię,

pozwalając pacjentom odtworzyć traumatyczne wydarzenie bez negatywnych objawów towarzyszących. Działania niepożądane tej terapii są mniej groźne i występują rzadziej niż w przypadku dotychczas używanych SSRI.

Wnioski: Powyższe obserwacje pokazują, że psychoterapia PTSD wspomagana MDMA jest obiecującą alternatywą dla dotychczasowych metod i niesie nadzieję pacjentom z najcięższym przebiegiem czy niereagującym na klasyczne leczenie.

Słowa kluczowe: MDMA, 3,4-metylenodioksymetamfetamina, psychoterapia wspomagana MDMA, PTSD

Introduction

Post-Traumatic Stress Disorder (PTSD) is a psychiatric disorder that can develop following exposure to traumatic events such as combat, sexual assault, natural disasters, or serious accidents [1]. It can manifest itself through 'avoidance', 'numbing', 'hyper-arousal' and the hallmark 're-experiencing' or 'intrusive symptoms', which include unwanted thoughts, flashbacks and nightmares [1]. PTSD is associated with the substance use disorders, depression and a significantly increased risk of suicide [2]. Symptoms listed above have profound and long-lasting effects on an individual's well-being and quality of life [3,4,5].

Presently, multiple guidelines issued by diverse agencies and professional organizations endorse a range of trauma-focused psychological interventions as the primary approach for addressing PTSD, which are variations of cognitive behavioural therapy. Moreover, these guidelines generally recognize the potential effectiveness of certain medication treatments in conjunction with psychotherapy [6].The first line in pharmacological treatment are the selective serotonin reuptake inhibitors (SSRIs). Nevertheless, a considerable proportion, ranging from 40% to 60%, of patients fail to exhibit a favourable response to these treatments [7]. There is an urgent need for innovative and cost-effective therapeutic approaches to address this issue [8].

In recent years, a unique therapeutic approach has gained attention and demonstrated remarkable potential for treating PTSD: 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy [9]. MDMA, commonly known as "ecstasy" or "Molly", is a synthetic psychoactive compound with a complex pharmacological profile that affects multiple neurotransmitter systems, including serotonin, dopamine, and norepinephrine [10]. In contrast to its recreational use, which is associated with party culture, MDMA's therapeutic use is distinct and carefully administered within a controlled clinical setting.

Studies have demonstrated that MDMA can facilitate fear memory extinction, influence fear memory reconsolidation (potentially via an oxytocin-dependent mechanism), and enhance social behaviour in animal models [11, 12]. The analysis of phase 3 trials investigating MDMA-assisted therapy for PTSD has revealed its potential to profoundly revolutionize PTSD treatment and warrants prompt evaluation for clinical implementation [13].

Material and methods

The purpose of this paper is to review publications from years 2020-2022 available on the PubMed platform about using MDMA in PTSD treatment, using words: MDMA, PTSD, MDMA and PTSD.

Discussion

MDMA Assisted Therapy (MDMA-AT)

MDMA acts as a catalyst for the therapeutic process, by decreasing patient's fear response to previous traumas and traumatic memories. This is the main premise for using the MDMA Assisted Therapy (MDMA-AT) in case of patients with PTSD [14]. This therapeutic method is based on the concept of the 'set and setting', which is similar to the one from early research with LSD. 'The set' describes the mindset of the patient and 'the setting' is the environment in which the session holds [17]. The patient's surroundings should be aesthetically pleasing even though it is taking place in clinical conditions [14]. Research show that in case of using psychedelic substances, like MDMA, music can take a great part in a success of the therapy [18]. That is why patients are often encourage to listen and focus on specially composed playlists during the session [14].

The scientific centre known for pioneering in psychedelic research – the Multidisciplinary Association for Psychedelic Studies (MAPS) – emphasises that the success of MDMA-AT greatly depends on the therapist and his 'sensitivity and talent' [15]. Patients are typically accompanied by a co-therapist pair, usually male and female. During the session, patients can need various kinds of support - from reassuring words to hugging – which can be physically and emotionally draining for just one therapist [16]. The therapists' role is to take care of patient's sense of security and wellbeing, to provide a proper preparation before session, to gain patient's trust and to provide guidance through the introspection process [15,17]. They are also responsible for maintaining the follow-up contact with patients and conducting patients' psychotherapy before and after [17].

MDMA session lasts from 5 to 8 hours. In the research, the substance is usually administered orally in doses from 75 to 125 mg, with a booster dose of half of the starting dose after 1 to 2 hours. The MDMA effects lasts from 4 to 6 hours. During several months of therapy, MDMA sessions occur 2 to 3 times in studies.

The impact on the therapeutic process

It is speculated that combining MDMA with psychotherapy creates a "window of tolerance", which allows patients to revisit and process traumatic events without being overwhelmed or encumbered by hyperarousal and dissociative symptoms. Additionally, MDMA-AT may enable recollection of traumatic memories with greater self-compassion and less PTSD-related shame and anger. Also, the therapeutic alliance may benefit from the use of MDMA due to its prosocial and interpersonal properties [13].

MDMA should not be taken on its own without proper support and pre-drug preparation. During this treatment PTSD symptoms may worsen due to deep processing of trauma, which may cause setbacks and increase risk of suicide for some patients [17].

It is important to point out that this treatment protocol did not exhibit increased risk of substance use, abuse or dependence during and 2 months after MDMA-AT. Moreover, studies show that, when used in controlled environment and with therapeutic support, MDMA has limited abuse potential [19].

How MDMA affects PTSD symptoms

MDMA's effects are primarily based on the increase of brain levels of serotonin, dopamine and norepinephrine [20] and enhance in oxytocin, vasopressin and cortisol levels [21].

On the grounds of findings of a Phase 3 clinical trial, change in CAPS-5 total severity score from baseline to 18 weeks after shows considerable improvement in PTSD symptoms. Moreover, in this study 28 of 42 (67%) patients from research group did not meet PTSD diagnostic criteria after the treatment, in contrast to 12 of 37 (32%) in the placebo group [13].

Research conducted on rodents point out that MDMA may modify the sensitivity to social reward [12] which is used in MDMA-AT during which patient is prompted to integrate emotional shifts associated with the session into their daily life. Lastly, MDMA's impact on amygdala leads to disruption of fear memories and allows restoration of the memory in a safe context [21].

Based on decreased CAPS scores, studies show significant improvement in PTSD symptoms that has a lasting effect even after the termination of MDMA-assisted therapy. Furthermore, patients reported other benefits, such as engagement in new activities, improved interpersonal, social and spiritual quality of life and openness to further psychotherapy [22]. According to one paper, this subjective positive changes suggest that MDMA-AT may promote Posttraumatic Growth (PTG) in PTSD patients and future trials should regard PTG as a secondary outcome of the treatment [23].

Sleep disturbances

Sleep disturbances (SDs) are one of the core PTSD features [26] and, along with recurrent nightmares, listed as diagnostic criteria with prevalence rates as high as 90% [25]. Although difficult to treat, research showed promising improvement in self-reported sleep quality in response to MDMA-assisted psychotherapy [24].

Sleep disturbances symptoms that present itself in individuals with PTSD are recurrent nightmares, insomnia, panicked awakenings with poor or no recollection of dream content, increase in physical movement during sleep and nightmare enactment [25]. Moreover, SDs may be precipitating and perpetuating for PTSD symptoms, which may result in impaired recovery [27]. Additionally, patients with significant SDs are prone to substance use, other health-related complaints, depression and suicidality [24].

Current methods used to improve sleep quality in PTSD patients focus on primary therapies that target PTSD with all its symptoms and pharmacological approach such as prazosin, doxazosin and terazosin. Nonetheless, those options are insufficient and findings show a need for new treatment which will target SDs and PTSD simultaneously [24].

MDMA may be the answer to this problem. Results from four Phase 2 trials show that MDMA-assisted therapy promotes improvements in PTSD symptoms and sleep disturbances measured at treatment endpoint. Based on PSQT (Pittsburgh Sleep Quality Index), 21 of 63 participants at 12-month follow-up did not meet SDs criteria. Moreover, the improvement in sleep quality positively impacted patients' PTSD symptoms severity. Contrary to this conclusion, some studies reported that MDMA may worsen insomnia in participants with PTSD and healthy controls, but this effect is temporary [24].

Alcohol and Substances Using

Alcohol and substance use disorders (ASUD) commonly co-occur with PTSD. There are few hypothesis behind this co-occurrence and some common pathways were established, like self-medication, shared liability, susceptibility and high-risk [28]. Comparing to patients with PTSD or ASUD alone, patients with PTSD+ASUD often react poorly to the treatment, which can even end up with failure or dropout [29].

Alcohol

Two studies showed that MDMA-AT can provide positive outcomes in case of patients with co-occurring PTSD and hazardous alcohol use. First paper focused on participants with severe PTSD, but without currently ongoing even mild AUD, which was its primary limitation [20]. However, the analyses showed that the level of alcohol consumption had significantly decreased, comparing to the baseline level, within the MDMA-AT group versus placebo group. They also suggested that this reduction may be uniquely associated with MDMA.

The main aim of the second study was to assess whether MDMA-AT is safe and tolerable for patients with AUD [30]. Participants were primary diagnosed with AUD as defined by DSM-IV, with severity on moderate to severe level. They also underwent a successful alcohol detoxication. Results showed that MDMA-AT was well tolerated by all patients. There were no unexpected adverse events and no medical interventions were required. Abnormal physiological disturbance was not reported, nor any significant neurocognitive impairments, even months after sessions. Patients also denied a desire to use illicit MDMA after the therapy. Participants coped well with the acute effects of the substance. Better tolerance for this therapy was also associated with minimal occurring of spiritual/mystical experience after taking MDMA. The study suggested that MDMA-AT may be a useful choice for AUD treatment not only because of the safeness of patients after the detoxication but also because of the positive impact on patients' symptoms. Avoidance of emotionally distressing thoughts and evoking memories of alcohol misuse were reduced, while the level of empathy for self and others was elevated. Moreover, the alcohol consumption over nine months after the MDMA-AT was significantly lower, comparing to current best treatments available in the area of the study [30].

Substances

Although, studies showed that MDMA-AT has positive impact on results of patients with co-occurring ASUD, the significant improvement relates more to alcohol using than other substances. In one study, DUDIT scores (The Drug Use Identification Test) after the therapy were lower for patients underwent MDMA-AT comparing to placebo group, but the differences were not statistically important [20]. However, authors associated this result with the absence of patients with current SUD diagnosis and the fact that the only active substance taken into account in this analysis was cannabis – other were excluded.

Importantly, MDMA-AT did not exhibit a risk for using or hazardous using of MDMA or addiction from this substance during the treatment and 2 months after the termination [20].

Interesting findings about correlation between MDMA using and occurring of PTSD symptoms were presented in two German studies on adolescents diagnosed with SUD [31, 32]. Both of them showed that adolescents displaying PTSD symptoms more frequently used MDMA. It was correlated with stronger coping motives and usually was an act of self-medication. Those studies also showed that with higher usage of this substance, the development of more severe avoidance symptoms or an escalation of sub-clinical PTSD symptoms might appear. However, one group of scientists emphasize that patients were taking MDMA in recreational setting, without proper therapeutic preparation and support and the exact components of the administered pills were unknown [31].

Eating Disorders

Eating disorders and PTSD have a high co-morbidity. As studies show, it ranges from 11% to even 52% [33]. This applies in particular to bulimia nervosa (BN) and binge eating disorders (BED). Both men and women with BN or BED have higher rates of trauma in their lifetime, especially a trauma perpetrated by others [34]. Research also indicate that anorexia nervosa (AN) can be triggered by psychological stress or stressful life events, which correlates with PTSD etiopathology [33]. Another study showed that patients suffering from PTSD can have 'clinically silent' ED symptoms – even without active purging or low BMI [35].

This fact encouraged scientists to start the research on the efficacy of the MDMA-AT on patients with PTSD and intercurrent EDs. In one analysis, MDMA-AT was able to demonstrate significant changes in EAT-26 (the Eating Attitudes Test) scores both in 'at risk' – EAT-26 score >11 at the beginning of the study – and 'clinical' – EAT-26 score ≥20 – groups, when after the placebo-AT the reliable changes were seen only in 'clinical' group [35]. The authors associated these results with anxiolytic and prosocial effects of the MDMA, which may be beneficial for both EDs and PTSD due to the disturbances of socio-emotional processing in both cases. Another study correlated positive impact of the MDMA-AT on ED patients with increase of psychological flexibility and awareness about behaviours, which are crucial in therapy for patients with EDs due to their cognitive rigidity [36].

However, authors of this paper brought attention to the limitations and risks of this therapy [36]. Firstly, participants cannot have recent restrictions or purging before the drug session, as well as they have to be mentally stable. Secondly, MDMA can cause medical complications such as loss of appetite, nausea and vomiting, which are very dangerous for ED patients, who are usually malnourished, and can lead to incl. hypotension or cardiac arrhythmias. Moreover, patients should be under careful

observation, because after the MDMA sessions, due to the acceleration of the process of overcoming psychological resistance, symptoms can be temporary exacerbated and this may generate mental instability and suicide risk.

Side effects and interactions

Research show that whilst MDMA is considered a safe and well-tolerated treatment option even in PTSD patients with coexisting conditions, it is not without side effects [13].

Recent data indicate that the most common include teeth grinding, jaw clenching, headache, lack of appetite, fatigue, dizziness and nausea. However, those symptoms are viewed as mild to moderate and they subside in time and without assistance [21].

Other more serious side effects that may occur are rhabdomyolysis, cardiac arrhythmias, hyperthermia, hyponatremia, acute renal failure and serotonin syndrome. Nevertheless, the likelihood of this health events is relatively low in a controlled environment and increases with higher doses of MDMA [20].

Also MDMA has a potential to cause higher heart rate and blood pressure, thereupon hypertension and some cardiovascular pathologies may be viewed as contraindications [14].

Drug interactions

Upon analysis, based on FDA drug safety surveillance data opioids, antidepressants (bupropion, citalopram, sertraline, venlafaxine), benzodiazepines, amphetamines and stimulants, anaesthetics, ethanol, MDMA metabolites or analogues, muscle relaxants and 2 dopamine antagonists (olanzapine and metoclopramide) were reported to increase risk of death when combined with MDMA. However, presented data was not collected in controlled clinical trials and refers to recreational MDMA – "ecstasy" without the knowledge of the purity and dose. Consequently, further studies should be carried out to evaluate possible drug-drug interactions [39].

Impact on economy

By the reason of many possible advantages of MDMA-AT in PTSD treatment, some USA researchers decided to analyse the costs of this therapy. There are just a few studies concerning this topic and the joint conclusion of them all is that providing MDMA treatment to patients with severe or treatment-resistant PTSD can be not only clinically beneficial but also cost-saving [8].

Two studies were based on different phases of the same trial conducted by MAPS but both indicated that expanding the access to MDMA-AT may be highly cost-effective and profitable for the healthcare system. In the phase 2 analysis from 2020 , $102 million savings to the healthcare system and 42.9 prevented deaths are estimated in 30 years [8]. The expected benefits from 2022 analysis of phase 3 of this trial are even more promising – 30-years savings has risen to $132.9 million and the number of averted deaths has increased to 61,4 [37]. The authors emphasized the limitations of those estimates and the first is uncertainty [8]. However, even if MDMA-AT costs will be higher than expected, this treatment remains cost-saving. The model used by the researchers also did not include the positive impact on families of PTSD patients and the socio-economic perks of improving the effectiveness of the PTSD therapy, such as decreasing number of substance abuse, involvement in attempting crimes and unemployment among PTSD patients [8]. They also assumed no relapses.

Another analysis estimated even higher benefits from expanding access to MDMA-AT to 25-75% of patients with severe and chronic PTSD [38]. Over 10 years, the expected number of prevented deaths oscillates between 43,618 and 106,932, which is more than the estimated number of prevented suicides by the availability of fluoxetine for depression. The savings for the healthcare system from MDMA-AT are estimated between $109 and $266 billion which is comparable to the medical expenditures from expanding access to smoking cessation programs [38].

The authors of those analysis brought out the role of other than economic and clinical factors in the process of adopting the MDMA-AT for PTSD [8, 38]. The most important one seems to be the removal of MDMA from the Controlled Substance Act and the fully legalization of MDMA-AT [38].

Conclusions

The MDMA-Assisted Therapy for PTSD may be a promising alternative for the current ways of treatment. The symptoms' improvement is seen in the most severe cases, when the past methods usually fail. Until now, clinical trials and research had very positive results not only in case of PTSD general symptoms, but also for co-occurrent disorders, such as sleep disturbances, ASUD, EDs. MDMA-AT seem to also be safer and have less severe side effects that currently most commonly used SSRIs. Further studies are needed to explicitly verify the effectiveness and safeness of MDMA-AT for PTSD patients. Without further research, it is also not possible for this therapy to enter the path to legalization and for this substance to be decriminalized for medical purposes. Currently, as for U.S. National Library of Medicine, 29 clinical trials are ongoing, with 6 at recruiting phase [40]. Most of them are led in the USA and Canada but a few also in European countries (UK, Norway, Germany, Netherlands, Switzerland and Portugal), Israel and Australia [40] - which is the nearest one to rescheduling the MDMA [41].

At the moment, there is no sign of launching a clinical trial for MDMA-AT in Poland.

Conflict of interest

The authors have declared no conflict of interest.

References:

1. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, Diagnostic and Statistical Manual of Mental Disorders, May 2013, doi: 10.1176/APPI.BOOKS.9780890425596.
2. LeBouthillier DM, McMillan KA, Thibodeau MA, Asmundson GJ. Types and Number of Traumas Associated With Suicidal Ideation and Suicide Attempts in PTSD: Findings From a U.S. Nationally Representative Sample. J Trauma Stress. 2015;28(3):183-190. doi:10.1002/jts.22010
3. Schnurr PP, Lunney CA, Bovin MJ, Marx BP. Posttraumatic stress disorder and quality of life: extension of findings to veterans of the wars in Iraq and Afghanistan. Clin Psychol Rev. 2009;29(8):727-735. doi:10.1016/j.cpr.2009.08.006
4. Giacco D, Matanov A, Priebe S. Symptoms and subjective quality of life in post-traumatic stress disorder: a longitudinal study. PLoS One. 2013;8(4):e60991. Published 2013 Apr 9. doi:10.1371/journal.pone.0060991
5. George KC, Kebejian L, Ruth LJ, Miller CW, Himelhoch S. Meta-analysis of the efficacy and safety of prazosin versus placebo for the treatment of nightmares and sleep disturbances in adults with posttraumatic stress disorder. J Trauma Dissociation. 2016;17(4):494-510. doi:10.1080/15299732.2016.1141150
6. Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults. https://www.apa.org/ptsd-guideline/ (accessed May 17, 2023).
7. 7. Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. JAMA. 2015;314(5):489-500. doi:10.1001/jama.2015.8370
8. Marseille E, Kahn JG, Yazar-Klosinski B, Doblin R. The cost-effectiveness of MDMA-assisted psychotherapy for the treatment of chronic, treatment-resistant PTSD. PLoS One. 2020;15(10):e0239997. Published 2020 Oct 14. doi:10.1371/journal.pone.0239997
9. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study [published correction appears in J Psychopharmacol. 2011 Jun;25(6):852]. J Psychopharmacol. 2011;25(4):439-452. doi:10.1177/0269881110378371
10. Carhart-Harris RL, Nutt DJ. Serotonin and brain function: a tale of two receptors. J Psychopharmacol. 2017;31(9):1091-1120. doi:10.1177/0269881117725915
11. Hake HS, Davis JKP, Wood RR, et al. 3,4-methylenedioxymethamphetamine (MDMA) impairs the extinction and reconsolidation of fear memory in rats. Physiol Behav. 2019;199:343-350. doi:10.1016/j.physbeh.2018.12.007
12. Nardou R, Lewis EM, Rothhaas R, et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. Nature. 2019;569(7754):116-120. doi:10.1038/s41586-019-1075-9
13. Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med. 2021;27(6):1025-1033. doi:10.1038/s41591-021-01336-3
14. Krediet E, Bostoen T, Breeksema J, van Schagen A, Passie T, Vermetten E. Reviewing the Potential of Psychedelics for the Treatment of PTSD. Int J Neuropsychopharmacol. 2020;23(6):385-400. doi:10.1093/ijnp/pyaa018
15. Mithoefer M, Mithoefer A, Jerome L, Ruse J, Doblin R, Gibson E, Ot'alora G. M, Sola E. A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder. 2017; ver. 8.1:7-8.
16. Greer GR, Tolbert R. A method of conducting therapeutic sessions with MDMA. J Psychoactive Drugs. 1998;30(4):371-379. doi:10.1080/02791072.1998.10399713
17. Sessa B, Higbed L, Nutt D. A Review of 3,4-methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy. Front Psychiatry. 2019;10:138. Published 2019 Mar 20. doi:10.3389/fpsyt.2019.00138
18. Kaelen M, Giribaldi B, Raine J, et al. The hidden therapist: evidence for a central role of music in psychedelic therapy [published correction appears in Psychopharmacology (Berl). 2018 Mar 26;:]. Psychopharmacology (Berl). 2018;235(2):505-519. doi:10.1007/s00213-017-4820-5
19. Nicholas CR, Wang JB, Coker A, et al. The effects of MDMA-assisted therapy on alcohol and substance use in a phase 3 trial for treatment of severe PTSD. Drug Alcohol Depend. 2022;233:109356. doi:10.1016/j.drugalcdep.2022.109356
20. Dunlap LE, Andrews AM, Olson DE. Dark Classics in Chemical Neuroscience: 3,4-Methylenedioxymethamphetamine. ACS Chem Neurosci. 2018;9(10):2408-2427. doi:10.1021/acschemneuro.8b00155
21. De Gregorio D, Aguilar-Valles A, Preller KH, et al. Hallucinogens in Mental Health: Preclinical and Clinical Studies on LSD, Psilocybin, MDMA, and Ketamine. J Neurosci. 2021;41(5):891-900. doi:10.1523/JNEUROSCI.1659-20.2020
22. Jerome L, Feduccia AA, Wang JB, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. Psychopharmacology (Berl). 2020;237(8):2485-2497. doi:10.1007/s00213-020-05548-2
23. Gorman I, Belser AB, Jerome L, et al. Posttraumatic Growth After MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder. J Trauma Stress. 2020;33(2):161-170. doi:10.1002/jts.22479
24. Ponte L, Jerome L, Hamilton S, et al. Sleep Quality Improvements After MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder. J Trauma Stress. 2021;34(4):851-863. doi:10.1002/jts.22696
25. Richards A, Kanady JC, Neylan TC. Sleep disturbance in PTSD and other anxiety-related disorders: an updated review of clinical features, physiological characteristics, and psychological and neurobiological mechanisms [published correction appears in Neuropsychopharmacology. 2019 Oct 7;:]. Neuropsychopharmacology. 2020;45(1):55-73. doi:10.1038/s41386-019-0486-5
26. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature?. Sleep Med Rev. 2008;12(3):169-184. doi:10.1016/j.smrv.2007.08.008
27. van Liempt S. Sleep disturbances and PTSD: a perpetual circle?. Eur J Psychotraumatol. 2012;3:10.3402/ejpt.v3i0.19142. doi:10.3402/ejpt.v3i0.19142
28. Hien DA, López-Castro T, Fitzpatrick S, Ruglass LM, Fertuck EA, Melara R. A unifying translational framework to advance treatment research for comorbid PTSD and substance

use disorders. Neurosci Biobehav Rev. 2021;127:779-794. doi:10.1016/j.neubiorev.2021.05.022
29. McCauley JL, Killeen T, Gros DF, Brady KT, Back SE. Posttraumatic Stress Disorder and Co-Occurring Substance Use Disorders: Advances in Assessment and Treatment. Clin Psychol (New York). 2012;19(3):10.1111/cpsp.12006. doi:10.1111/cpsp.12006
30. Sessa B, Higbed L, O'Brien S, et al. First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. J Psychopharmacol. 2021;35(4):375-383. doi:10.1177/0269881121991792
31. Basedow LA, Wiedmann MF, Roessner V, Golub Y, Kuitunen-Paul S. Coping motives mediate the relationship between PTSD and MDMA use in adolescents with substance use disorders. Addict Sci Clin Pract. 2022;17(1):46. doi:10.1186/s13722-022-00329-y
32. Basedow LA, Kuitunen-Paul S, Wiedmann MF, Roessner V, Golub Y. Self-reported PTSD is associated with increased use of MDMA in adolescents with substance use disorders. Eur J Psychotraumatol. 2021;12(1):1968140. doi:10.1080/20008198.2021.1968140
33. Swinbourne JM, Touyz SW. The co-morbidity of eating disorders and anxiety disorders: a review. Eur Eat Disord Rev. 2007;15(4):253-274. doi:10.1002/erv.784
34. Mitchell KS, Mazzeo SE, Schlesinger MR, Brewerton TD, Smith BN. Comorbidity of partial and subthreshold ptsd among men and women with eating disorders in the national comorbidity survey-replication study. Int J Eat Disord. 2012;45(3):307-315. doi:10.1002/eat.20965
35. Brewerton TD, Wang JB, Lafrance A, et al. MDMA-assisted therapy significantly reduces eating disorder symptoms in a randomized placebo-controlled trial of adults with severe PTSD. J Psychiatr Res. 2022;149:128-135. doi:10.1016/j.jpsychires.2022.03.008
36. Brewerton TD, Lafrance A, Mithoefer MC. The potential use of N-methyl-3,4-methylenedioxyamphetamine (MDMA) assisted psychotherapy in the treatment of eating disorders comorbid with PTSD. Med Hypotheses. 2021;146:110367. doi:10.1016/j.mehy.2020.110367
37. Marseille E, Mitchell JM, Kahn JG. Updated cost-effectiveness of MDMA-assisted therapy for the treatment of posttraumatic stress disorder in the United States: Findings from a phase 3 trial [published correction appears in PLoS One. 2022 Jun 2;17(6):e0269623]. PLoS One. 2022;17(2):e0263252. Published 2022 Feb 25. doi:10.1371/journal.pone.0263252
38. Avanceña ALV, Kahn JG, Marseille E. The Costs and Health Benefits of Expanded Access to MDMA-assisted Therapy for Chronic and Severe PTSD in the USA: A Modeling Study. Clin Drug Investig. 2022;42(3):243-252. doi:10.1007/s40261-022-01122-0
39. Cohen IV, Makunts T, Abagyan R, Thomas K. Concomitant drugs associated with increased mortality for MDMA users reported in a drug safety surveillance database. Sci Rep. 2021;11(1):5997. Published 2021 Mar 16. doi:10.1038/s41598-021-85389-x
40. https://www.clinicaltrials.gov/ct2/results?cond=ptsd&term=mdma&cntry=&state=&city=&dist=
41. https://adf.org.au/insights/mdma-ptsd/ . Published 2023 Mar 7.

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