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Psychedelics as a treatment for patients with post-traumatic stress disorder (PTSD)

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Abstract

Introduction and purpose: Post-traumatic stress disorder is a psychiatric condition following an extreme event that causes a near death of an involved individual. Since conventional treatments using selective serotonin reuptake inhibitors do not consistently yield therapeutic success, alternative substances are being explored as potential solutions. This study aims to compile information regarding the outcomes of utilizing psychedelics in individuals diagnosed with PTSD.

Brief description of the state of knowledge: In July 2023, after a number of clinical trials and 20-year-long efforts to overturn the impact of a prohibition, Australia became the first country to allow doctors, in clinical development and under strict control, to use the 3,4-methyl enedioxy methamphetamine (MDMA) commonly known as ecstasy, as well as psilocybin in patients with post-traumatic stress disorder or depression [1]. There is a noticeable annual growth of inquiries on PubMed involving the keywords "psychedelics" and "therapeutic", amounting to 92 in 2000 and topped by 738 searches in 2023, whereas the total number of results consists of 8415 positions. Therapeutic effects of psychedelics are becoming more recognized over time.

Summary: Post-Traumatic Stress Disorder (PTSD) is a complex condition that affects both the psychological and somatic aspects of the body. Thus, a multidimensional intervention is indicated. The use of psychedelics might contribute to improvements not only in the severity of PTSD but also in depression or pain. Further research on a larger group of participants should be carried out to assess the potential role of psychedelics in conventional medicine in the future, alongside psychotherapy.

Key words: PTSD; trauma; psychedelics; MDMA; treatment

Introduction

As outlined in the DSM-5, post-traumatic stress disorder (PTSD) is a mental health condition resulting from experiencing a traumatic event, specifically involving actual or threatened death, severe injury, or sexual violence [2], around 1-8% of the population to varying degrees, is affected [3]. In an era of several political conflicts around the world, mass migration, and increased violence, it seems essential to research and broaden the spectrum of tools, apart from those in common use, that could help the patients under diverse conditions effectively deal with PTSD, whose symptoms encompass dissociative reactions, flashbacks, ongoing avoidance of trauma-related triggers or social contacts, aggressiveness, feelings of guilt, and more [4]. Although the first-line treatment is selective serotonin reuptake inhibitors (SSRIs) [5], roughly 40% to 60% of individuals do not exhibit any positive response to these substances [6, 7]. Considering that for patients with other psychiatric conditions, an estimated past-year comorbidity circulates around 57.9% [8], and what is more, in many cases, especially in a warzone or during a migration crisis, the availability of cognitive-behavioral psychotherapy might not always be present, there is a clear need for an effective, attainable, fast-acting and relatively safe medication. The history of using psychedelics, such as psilocybin, especially in a religious and magical context, dates back thousands of years ago [9], while others like MDMA were not synthesized until the first half of the 20th century [10]. The actions undertaken by the U.S. Congress in the 1960s and 1980s along with other governments and health-related organisations around the globe, led to an absolute ban and marginalisation of numerous psychedelics and their researchers for the upcoming 40 years [11]. However, th. Clinical trials on psychedelics as a way of treating various psychiatric conditions have recently been conducted not only in Australia [1], but also in Switzerland [12], the United States, Israel, and several other countries, indicating a growing interest in the use of

these substances in the medical field. Any further benefits and risks must therefore be weighed; however, given the illicit status of psychedelics, undertaking research may pose legal and ethical challenges.

Aim

The aim of this study is to gather and analyse either the current state of knowledge and the newest studies, increase awareness, and start a discussion over the potential use and risks of the three analysed psychedelics in patients with PTSD.

Methods

The study involved searching freely accessible databases like PubMed, the National Library of Medicine, Clinical Trials, Google Scholar, or Cochrane, using keywords such as 'PTSD', 'trauma', 'psychedelics', 'MDMA', and 'treatment'. Articles were initially selected based on their title and, subsequently, on their abstract. Ultimately, only articles written in English related to potential PTSD treatment using chosen psychedelics were included in the study.

Ketamine

Glutamate serves as the primary excitatory neurotransmitter in the central nervous system [13], whereas ketamine, acting as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor, has been clinically proven to trigger a swift onset of antidepressant effects in humans by influencing the efficacy of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor (AMPA) in neuronal networks [13, 14]. The clinical use of a racemic mixture containing S- and R-ketamine began in 1970, and its steady antidepressant effects may result from compatible synaptic changes described by various, not mutually exclusive hypotheses [15, 16]. However, alongside its antidepressant effects, ketamine may debilitate attention, associative skills, and memory [15, 17].

MDMA

3,4-Methylenedioxyamphetamine (MDMA), commonly known as ecstasy, first appeared in 1912 [18]. Initially intended for stopping bleeding, MDMA made its way into psychiatry in no time due to its mechanism of action involving the release of serotonin, norepinephrine, oxytocin, cortisol, and dopamine. The mechanism not only ensures its haemostatic character but also affects the function of the cerebrum by decreasing the blood flow through the structures of the limbic system, such as the amygdala, directly deactivating the feelings of fear, sorrow, anxiety, and trauma [18,19], on the contrary, fostering neuronal plasticity, and promoting feelings known as positive such as joy, cheerfulness, talkativeness, energy, friendliness, increased mood, and empathy [19, 20]. Adverse effects resulting from an excessive release of the mentioned neurotransmitters and hormones include the symptoms of serotonin syndrome: tachycardia, increased blood pressure, diaphoresis, or mydriasis, which seem to be the most serious obstacle in the process of introducing MDMA as a therapeutic option [20, 21].

Limbic system

Psilocybin

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine), found in a numerous group of psychoactive mushrooms, mostly *Psilocibes*, had been used for thousands of years for religious and magical purposes and was first synthesized and described in the 1950s by an employee of Sandoz Laboratories [22, 23]. Its mechanism of action, as a 5-HT(2A) agonist, is perceived as an explanation for the psilocybin's mood-enhancing, anti-depressive, and psychedelic properties [24, 25, 26], researched clinically on a wider scale thanks to the temporary and more permanent effects on the psyche not until the 2010s [26, 27].

Results

From 2016 to 2020, Abdullah et al. [28] randomized 158 individuals suffering from moderate to severe PTSD and depression into three study groups: placebo, low dose of ketamine (0,2

mg/kg), and standard dose of ketamine (0,5 mg/kg). There were, in total, 8 infusions of ketamine or placebo two times a week and later observations once a week for the four upcoming weeks after the last administration. PCL-5, CAPS-5, CADSS, and PANSS scales were used in the process. The study confirmed neither early ($p=0.17$) nor late ($p=0.28$) effectiveness of both doses of ketamine in alleviating PTSD symptoms compared to placebo; however, a clear early- and late-anti-depressive effect of ketamine has been observed.

Randomized assignment of 30 participants to either the 0.5 mg/kg ketamine hydrochloride group or the 0.045 mg/kg midazolam group, with the aim of controlling PTSD severity through the CAPS-5 and MADRS scales, along with monitoring substance-related adverse effects was conducted by Feder et al. [29]. Over the course of 14 days, each group received a total of 6 infusions. The study's conclusion indicated a notable improvement in CAPS-5 (at week 1 ($p = 0.030$) and week 2 ($p = 0.004$) and MADRS scales for the ketamine group compared to the midazolam group, with 67% of the ketamine group responding to the intervention, which is an over three times higher result than that observed in the second group. The ketamine group also demonstrated a longer time until the loss of response. No severe side effects were observed.

Dadabayev et al. [30] administered a single intravenous injection of either ketamine (0.5 mg/kg) or ketorolac (15 mg) to 41 patients categorized into four randomized groups, including those with chronic pain (CP) with or without post-traumatic stress disorder (PTSD). Subsequently, the IES-R and VAS scales were assessed up to 7 days after the initial drug administration. Unlike the CP+ PTSD+ group, the CP+ PTSD- group provided with ketamine exhibited less pain in the VAS score compared to ketorolac ($p < 0.001$). In the CP+ PTSD+ group, both substances exerted a similar overall improvement in the PTSD symptom IES-R score ($p = 0.03$) either 1 or 7 days after the intervention, but no effect of the chosen substance was proven ($p > 0.05$).

Next trial, conducted by Mitchell et al. [31], randomized 91 individuals, assigning 46 to the MDMA-assisted therapy group and 45 to the placebo-assisted therapy group. Participants obtained either an 80 mg dose and later 40 mg after 1.5 to 2.5 hours, 120 mg and later 60 mg, or a placebo. Over the course of an eighteen-week study, the MDMA group exhibited a significant reduction in CAPS-5 scores, with a mean change of -24.4 points, compared to only -13.9 points in the placebo group. Additionally, the effectiveness of reducing depression was demonstrated in the BDI-II, with an average change of -19.7 points for MDMA and -10.8

points for the placebo ($p = 0.0026$). Only mild to moderate side effects were observed in the MDMA group, whereas three serious adverse effects emerged in the placebo group. The placebo group reported two instances of suicidal behavior, one case of suicidal ideation, and five other instances of suicidal interests, while the MDMA group reported three instances of other suicidal interests.

Another study was performed by Mithoefer et al. [32] from 2010 to 2015, where 26 individuals were randomized into three groups of 7, 7, and 12 participants, respectively, receiving psychotherapy along with 30 mg, 75 mg, and 125 mg of MDMA. Unlike the 30 mg group, the 75 mg and 125 mg groups showed a short-term improvement in CAPS-IV scores. The doses were generally well-tolerated, with 85 reported side events, including four serious ones. In the long term, after 12 months, the CAPS-IV scores remained significantly reduced following the administration of the full drug dose.

Oehen et al. [33] randomly assigned 8 individuals to the 1st group receiving 125 mg of MDMA, followed by 62.5 mg after 2.5 hours, and 4 individuals to the 2nd "active placebo" group, which received 25 mg of MDMA, followed by 12.5 mg after 2.5 hours. In both groups, the administrations were accompanied by psychotherapy sessions. An effect over time ($p = 0.002$) was observed in the 1st group, with a 23.5% drop in CAPS scores as well as a drop in PDS scores. In contrast, the 2nd group presented a rise in PDS scores.

Table 1. Studies on psychedelics use in PTSD

Study	Year	Substance	Dose	Effects on PTSD severity	Other information
Abdullah et al. [28]	2022	Ketamine	0,2 mg/kg and 0,5 mg/kg	No effect confirmed	Anti-depressive activity observed. One of the largest groups of participants. The study was ended because of the COVID-19 pandemics
Feder et al. [29]	2021	Ketamine	0.5 mg/kg	Improvement in CAPS-5 and MADRS scales for PTSD	Relatively small group of participants
Dadabayev et al. [30]	2020	Ketamine	0.5 mg/kg	Reduction of symptoms not linked to a type of medication used in this study	Relatively small group of participants
Study	Year	Substance	Dose	Effects on PTSD severity	Other information
Mitchell et al. [31]	2021	MDMA	80mg and 40mg or 120mg and 60 mg	Significant reduction in CAPS-5 scores	Additional antidepressive effect. Transient hypertension in MDMA group. Suicidality not increased in MDMA group.
Mithoefer et al. [32]	2018	MDMA	30 mg, 75 mg, and 125 mg	Improvement in CAPS-4 score. Long-lasting effect after a full-dose.	No significant side effects
Oehen et al [33]	2012	MDMA	12,5 mg, 25 mg, 62,5 mg, 125 mg	Improvement in the full-dose group.	Relatively small group of participants

There is an insufficient number of credible studies regarding the use of psilocybin in patients with PTSD. Further clinical trials are required, as psilocybin may have the potential to alleviate symptoms in various psychiatric conditions [34]. Several clinical trials on psilocybin use in PTSD are now being conducted in the United States, the United Kingdom, and Canada. The results are supposed to be published in 2024–2025.

Discussion

The results of the studies presented in this review on the use of psychedelics such as MDMA, ketamine, and psilocybin provide grounds for cautious optimism. Although not all the results were consistent, the significance of alleviating the symptoms of PTSD in most studies was proven. There is a growing amount of literature on the topic, ongoing debates in many countries regarding the legal status of these substances, and an increasing number of pieces of evidence supporting their potential in medicine. However, a limitation of reviewed studies is most often a small number of participants [29, 30, 31, 32, 33], unlike Abdullah et al. [28], who conducted one of the largest studies in this category. The low number of available studies and clinical trials halts the integration of psychedelics into therapeutic processes. Another crucial aspect are the side effects of specific substances, such as transient hypertension, leading to the exclusion of participants from ongoing studies and restricting the potential use of psychedelics in groups of cardiovascular, elderly, and severely ill patients. PTSD is a complex psychiatric condition, and while existing treatment methods do not always guarantee complete therapeutic success, the findings of the reviewed studies prove the significant efficacy of psychedelics in treating this condition. Given the increasing demand for effective therapies, especially in the current political climate, any new review, including this one, on novel therapeutic options is of significant importance. In the future, there should be increased investment to assess on a larger scale the risks and efficacy of psychedelic therapy, participant groups in clinical trials should expand, and, finally, the introduction of the most effective and safe psychedelic substances for PTSD resistant to traditional treatment and therapy should be considered.

Summary (conclusions)

Psychedelics such as MDMA, ketamine, or psilocybin are linked to a reduction in the symptoms and severity of PTSD, depression, or chronic pain. More research, involving a larger participant group, and a more reliable assessment of risks and benefits are needed to recommend considering any of these substances as an additional future therapeutic possibility should conventional therapy options fail.

Authors contributions

Krzysztof Marcinkowski: Conceptualization, Writing - rough preparation, Methodology, Investigation

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Karolina Strus: Supervision, Visualisation

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Roksana Zdunek: Supervision, Writing - rough preparation

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All authors have read and agreed with the published version of the manuscript.

Conflict of interest

The authors report no conflict of interest.

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