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Psychedelic Therapies in the Management of Post-Traumatic Stress Disorder: A Narrative Review

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Abstract:

Background. Post-Traumatic Stress Disorder (PTSD) is an important public health challenge typically treated with trauma-focused psychotherapy and Selective Serotonin Reuptake Inhibitors (SSRIs). However, high rates of residual symptoms associated with these standard treatments have led to a renewed interest in psychedelic-assisted therapies.

Aim. This review attempts to examine emerging psychedelic therapies in the management of PTSD, with a primary focus on 3,4-methylenedioxymethamphetamine (MDMA), psilocybin, and ketamine.

Material and methods. A literature search was carried out using PubMed, Google Scholar, and Scopus to identify relevant studies using keywords such as 'PTSD', 'MDMA', 'psychedelics', 'ketamine', 'psychedelic-assisted therapy', 'neuroplasticity', and 'fear extinction'.

Results. Psychedelics induce neuroplasticity and augment fear extinction, primarily through the AMPAR-BDNF-TrkB-mTOR pathway and 5-HT2A receptors. MDMA-assisted therapy demonstrates high efficacy, with a trial showing that 67% of participants no longer met PTSD criteria at the study endpoint. Psilocybin effectively treats common comorbidities like anxiety and treatment-resistant depression. Ketamine offers rapid symptom alleviation, making it notably beneficial for treatment-resistant cases with a high risk of self-harm and suicide.

Conclusions. Psychedelic therapies, particularly MDMA-assisted therapy, represent a potential breakthrough by targeting the underlying causes of PTSD rather than merely suppressing symptoms. In spite of current regulatory problems, they hold meaningful promise, pointing out the need for standardized treatment protocols to ensure safety and reproducibility in future research.

Keywords: Post-Traumatic Stress Disorder, MDMA, psilocybin, ketamine, psychedelic-assisted therapy, neuroplasticity.

1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a disorder precipitated by a traumatic event, characterized by persistent symptoms such as anxiety, re-experiencing the trauma through nightmares or flashbacks, and avoidance behaviours lasting for more than one month (1). The persistence of these symptoms is deeply rooted in neurobiological alterations, notably the hyperactivity of the amygdala (2).

PTSD remains an important public health challenge; a World Health Organization study has shown that the lifetime prevalence of this disorder is 2.3% in upper-middle-income countries,

and 2.1% in lower-middle-income countries (3). Other studies show that PTSD can possibly affect 25-35% of people who have suffered a serious trauma (2), and as much as 8% of the general population (4).

Currently, the first-line treatment for PTSD is trauma-focused psychotherapy, including cognitive-behavioural therapy (CBT), exposure-based therapy, and eye movement desensitization and reprocessing therapy (EMDR). Studies reliably show that trauma-focused psychotherapy yields greater efficacy compared to the standard pharmacological treatments, such as Selective Serotonin Reuptake Inhibitors (SSRIs) (5–9). However, this approach is troubled by a high rate of residual symptoms among patients subjected to this treatment (10). Furthermore, trauma-focused psychotherapies are frequently hindered by a substantial dropout rate, as many patients find it psychologically intolerable to repeatedly confront their trauma during exposure sessions (2). Pharmacological interventions like SSRIs also present noteworthy challenges, including a delayed onset of action, systemic side effects, and an important proportion of patients exhibiting treatment resistance (4).

The limitations of existing treatments have caused renewed interest in psychedelic-assisted therapies, which were initially explored in the middle of the 20th century before being halted by regulatory restrictions (11,12). Unlike standard daily pharmacotherapy, psychedelics administered in a controlled therapeutic setting are hypothesized to induce transient states of enhanced neuroplasticity and facilitation of psychotherapy (12).

The most important acceleration of research in this area happened with the FDA granting breakthrough therapy designation to 3,4-methylenedioxymethamphetamine (MDMA) for PTSD (13). This narrative review will examine the emerging psychedelic therapies in the management of PTSD, with the greatest focus on MDMA, psilocybin, and ketamine. It aims to evaluate their efficacy, mechanisms of action, and safety profile as well as their viability as treatments for PTSD.

2. Methodology

A comprehensive literature search was carried out utilizing PubMed, Google Scholar, and Scopus databases to identify relevant articles published up to May 2026. The search strategy employed combinations of Medical Subject Headings (MeSH) terms and free-text words, linked by Boolean operators (AND, OR). The search queries included variations of the following keywords: “PTSD”, “post-traumatic stress disorder”, “MDMA”, “psilocybin”, “ketamine”, “psychedelics”, “psychedelic-assisted therapy”, “LSD”, “ayahuasca”, “ibogaine”, “mescaline”, “neuroplasticity”, “fear extinction”, “efficacy”, and “safety”.

The inclusion criteria were restricted to peer-reviewed articles published in English. Initial screening was performed based on titles and abstracts to assess relevance. Subsequently, full-text articles were evaluated for their contribution to understanding the clinical efficacy, mechanisms of action, and safety profiles of MDMA, psilocybin, and ketamine in the context of PTSD.

2.1. AI.

AI was utilized for assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI was used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that the AI tool was used strictly as assistive instrument under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by humans. The AI tool served primarily to enhance efficiency in linguistic refinement, rather than replacing human judgment in the analytical process.

3. Neurobiological mechanisms

The classical psychedelics, such as LSD, psilocybin, ayahuasca, or mescaline, exert their primary psychoactive effects through serotonin 2A receptor (5-HT2A) agonism. They are non-selective as most psychedelic drugs are also serotonin 2B receptor (5-HT2B) and serotonin 2C (5-HT2c) receptor agonists (14). These substances, through 5-HT2A receptor-expressing glutamatergic neurons, also stimulate the release of brain-derived neurotrophic factor (BDNF) (15). In contrast, MDMA and ketamine are considered non-classical psychedelics, with distinct primary targets (16). MDMA, a member of the entactogen group, activates the aforementioned 5-HT2A, 5-HT2B, and 5-HT2C receptors by blocking serotonin reuptake, therefore augmenting its concentration in the synaptic cleft. MDMA also blocks norepinephrine and dopamine reuptake (16–18), as well as, through serotonergic activity, promoting the release of oxytocin and BDNF (15,17,19). Ketamine, on the other hand, is a dissociative anesthetic, an N-methyl-D-aspartate (NMDA) receptor selective antagonist, blocking the receptors on GABAergic interneurons in the cortex and hippocampus. This way, through activation of glutamatergic neurons directly acting upon α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) it also augments the BDNF activity (15,20).

3.1. Neuroplasticity

The aforementioned substances, mainly through the AMPAR-BDNF-TrkB-mTOR pathway, induce neuroplasticity (15) – a property that classifies them as psychoplastogens. Although

SSRIs activate the same pathway, their effects are gradual and less stable than in the case of psychoplastogens (15). Other observed effects of psychedelic drug administration include an increase in the expression of neuroplasticity-related genes, elevated dendritic spine density, and promoted proliferation of dendrites (14). This state of increased plasticity is highly beneficial in the treatment of various psychiatric disorders, and especially PTSD, as some studies suggest that a malfunctioning BDNF signalling is a part of its pathology – a decrease in neuroplasticity prevents patients from replacing maladaptive fear memory associations (17).

3.2. Fear extinction

One of the most effective therapies for PTSD these days, exposure-based therapy relies heavily on fear extinction learning, which is a process of diminishing a previously conditioned fear response through repeated exposure to known fear-inducing stimuli in a safe environment (20). Its molecular mechanism involves the AMPAR-BDNF-TrkB-mTOR pathway, 5-HT2A receptors, and oxytocin receptors (19), all of which are acted upon by various psychedelic drugs we mentioned earlier. Having noted all above, MDMA is a highly efficient fear extinction augmenting agent, as it also diminishes fear response from the amygdala (20). Other drugs having documented fear extinction effects include: psilocybin, ketamine, LSD, mescaline, and ayahuasca (20–25).

4. Psychedelic therapies

In this section, we will review various substances mentioned above that have proven to be effective in the management of PTSD. Current evidence is summarized in Table 1.

Table 1. Current evidence regarding psychedelic therapies in PTSD.

Intervention	Authors	Phase & Trial Design	Target population	Key Clinical Findings
MDMA-AT	Mitchell et al., 2021 (26)	Phase III, double-blind, RCT	Severe PTSD	67% of MDMA group no longer met PTSD criteria; significant CAPS-5 scores drop
MDMA-AT	Mitchell et al., 2023 (27)	Phase III, double-blind, RCT	Moderate to Severe PTSD	Confirmed above study's efficacy; no major safety signals

Ketamine IV	Feder et al., 2014 (28)	Phase II, double-blind crossover	Chronic PTSD	Rapid symptom reduction; significantly greater CAPS-5 scores reduction vs. midazolam.
Ketamine IV	Feder et al., 2021 (29)	Phase II, double-blind, RCT	Chronic PTSD	67% response rate after repeated infusions; median duration of 27.5 days

MDMA, 3,4-methylenedioxymethamphetamine; MDMA-AT, MDMA-assisted therapy; RCT, randomized control trial; PTSD, post-traumatic stress disorder; IV, intravenous; CAPS-5, Clinician-Administered PTSD Scale for DSM-5.

4.1. MDMA-Assisted Therapy

MDMA-assisted therapy (MDMA-AT) currently is the most promising kind of psychedelic treatment in PTSD. However, its trajectory recently encountered a regulatory hurdle when the FDA issued a Complete Response Letter declining its immediate approval. The agency's reservations mainly focus on the need for more rigorous reporting of both positive and negative adverse events to ensure strong safety data (30,31). In spite of this setback, MDMA-AT remains a highly valuable prospective treatment. The landmark evidence is a randomized, double blind, placebo-controlled phase 3 trial by Mitchell et al. (26,27), which explores the efficacy and safety of the drug in patients with severe PTSD, including those with common comorbidities. In these trials, MDMA-AT was found to attenuate scores in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and in the Sheehan Disability Scale (SDS). Critically, 67% of participants receiving MDMA-AT no longer met PTSD diagnostic criteria at study endpoint, compared with 32% in the placebo group. Notably, the drug did not promote suicidality, abuse potential, cardiovascular risk, or other important adverse events (32), which is confirmed by other authors (16). The researchers speculate that the drug opens a "window of tolerance", enabling the patients to process traumatic content, thus facilitating the psychotherapy (27,33). Other beneficial effects of MDMA include a reduction of negative affect and facilitation of adaptive post-trauma social behaviors – notably even when the trauma exposure occurs under

the influence of MDMA – such conclusions were drawn in an observational study by Netzer et al. (34), investigating the participants of a rave held in the Gaza Envelope region, attacked by Hamas. The ravers intoxicated by MDMA had reduced psychological distress, higher sociality, and improved sleep quality in the post-traumatic period (34). Another important effect of MDMA is the enhancement of a therapeutic alliance (19). Importantly, a general consensus on the safety of treatment is that in a controlled environment, such as MDMA-AT, most of the risks of the substance's adverse effects are mitigated (16,35).

4.2. Psilocybin-Assisted Psychotherapy

Most commonly, the treatment protocol of a psilocybin-assisted psychotherapy (PAP) consists of therapy under the influence of the drug, but the therapist is less involved over the course of the session than in MDMA-AT (35). Although preclinical studies, as discussed above, provide strong mechanistic evidence for the potential beneficial impact of psilocybin on PTSD treatment, there is limited direct clinical evidence for its efficacy in the disorder (19,36,37). To date, only one study found a decline in PTSD severity in patients subjected to PAP (38). Nevertheless, it has proven to be useful in the treatment of depression and anxiety, conditions that often co-occur with PTSD (19); psilocybin excels at reducing symptoms in treatment-resistant depression, all while preventing suicide-related ideations and behavior (19,35,37,39,40). Furthermore, preliminary data suggest PAP may enable the patients to retrieve and process traumatic memories (35,41).

4.3. Ketamine

A study by Feder et al. (29) found that a repeated intravenous treatment with ketamine yields a substantial efficacy rate, with 67% of patients responding to the treatment. The patients receiving ketamine showed a significant drop in PTSD CAPS-5 assessment. Furthermore, the therapeutic benefits lasted a median of 27.5 days after the final infusion.

In other studies, however, ketamine was found to be ineffective and exacerbating the symptoms in early PTSD, with its effectiveness proven only for treating chronic PTSD (41,42). There has also been a study that has tried to use ketamine to treat PTSD in a protocol similar to MDMA-AT and PAP – an administration of ketamine combined with mindfulness-based cognitive therapy (Ket-MBCT). The results were promising as the patients who received Ket-MBCT had a long-lasting improvement in PTSD symptoms (43). Ketamine could also be beneficial for patients with treatment-resistant PTSD, who are at a high risk for self-harm and suicide, as it acts quickly and alleviates the symptoms, thus preventing them from acting on suicidal impulses (35,36).

4.4. Other classic psychedelics: LSD, mescaline, and ayahuasca

The clinical application of other classic serotonergic psychedelics for PTSD remains underexplored in modern controlled trials (41). However, given their shared neurobiological mechanisms of action, particularly 5-HT2A agonism and psychoplastogenic effects, they are hypothesized to offer therapeutic benefits comparable to psilocybin. Current epidemiological and observational knowledge provides preliminary evidence that these compounds can effectively reduce anxiety and depressive symptoms, facilitate complex trauma processing (40), as well as reduce likelihood of suicidal behavior (44).

4.5. Safety and Adverse Effects

MDMA is regarded as a safe substance, with a safety profile similar to SSRIs (33). Most adverse effects are transient, such as an increase in blood pressure, muscle tightness, nausea, decreased appetite, insomnia, and anxiety (18,33). Many of previously described adverse effects relate to recreational use of the drug and were not found in the clinical setting (18,41). Nevertheless, safety protocols are needed as the substance could possibly induce hyperthermia, dehydration, hyponatremia, serotonin syndrome, rhabdomyolysis, disseminated intravascular coagulation, and severe hepatotoxicity, thus underlining the need for a close monitoring of the patients (33,41).

The main risk entangled with the use of psilocybin is its potential to accelerate the development of latent schizophrenia (41). Acute adverse reactions are similar to those of MDMA and tend to be transient and limited (41).

The side effects of ketamine are also transient and mild, they include nausea, headache, tachycardia, elevated blood pressure, and dissociation. Ketamine may as well induce dysuria or urgency. The drug must be used under supervision, as at high doses it may lead to long-term impairments in cognition (45).

5. Current State of Psychedelic Research in PTSD

Several ongoing clinical trials are currently investigating the efficacy and safety of psychedelic therapies for PTSD (*Table 2)*.

Table 2. Current clinical trials investigating psychedelic therapies in PTSD.

Intervention	Study Number, Location	Phase & Trial Design	Target population
Inpatient high-intensity MDMA-AT	NCT06954025, Netherlands	Phase II, Open-Label Pilot Study	Treatment-refractory PTSD with current moderate to severe PTSD which did not benefit from at least two

			evidence-based psychotherapies
MDMA-AT	NCT06418178, the United States	Phase II	U.S. military veterans with a PTSD diagnosis
MDMA-AT vs. low dose d-amphetamine-assisted therapy	NCT05790239, the United States	Phase II, Randomized Double-Blind, Single-Site, 2-Arm Study	U.S. military veterans with at least moderate PTSD
Psilocybin administration *per os*, without assisted therapy	NCT05243329, Canada	Phase II	Treatment-resistant PTSD symptoms (CAPS-5 score ≥ 30), after at least 3 months of prior SSRI or SNRI treatment in addition to at least 4 months of psychotherapy
Psilocybin-assisted Psychotherapy	NCT06888128, the United States	Phase II	U.S. military veterans with PTSD with CAPS-5 score of at least 23
Psilocybin-assisted Psychotherapy	NCT05554094, the United States	Phase II, Open-Label	U.S. military veterans with PTSD with CAPS-5 score of at least 35

Source: findclinicaltrials.eu (46)

PTSD, Post-Traumatic Stress Disorder; U.S., United States; MDMA-AT, MDMA-assisted Therapy; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor.

6. Discussion

The use of psychedelic drugs in the management of PTSD could potentially shift the physicians' focus from suppressing the disease symptoms to acting directly upon the source of trauma. The psychedelics excel at promoting neuroplasticity and fear extinction mechanisms, with notable differences in mode of action between different substances. MDMA is the most useful for psychedelic-assisted psychotherapy as it enhances the therapeutic alliance and eases the fear response associated with retrieving the traumatic memories. Ketamine is characterised by a rapid onset of action, making it perfect for treatment-resistant cases with a high risk of suicidality. Classic psychedelics such as psilocybin, LSD, mescaline, and ayahuasca remain relatively unresearched in the domain of the management of PTSD, but they work exceptionally well for the comorbidities such as depression or anxiety.

Despite the mechanistic evidence, psychedelic drugs in psychiatric care face important challenges, especially with the recent regulatory setbacks. There is a need for standardized protocols to ensure the safety and reproducibility of future studies.

7. Conclusion

Psychedelic therapies in the management of PTSD represent a potential breakthrough approach to the treatment of the disorder, transitioning the focus from chronic symptom mitigation to the active resolution of underlying trauma. Among the substances reviewed, MDMA-AT currently demonstrates the strongest evidence base, exhibiting a great efficacy. Furthermore, classic psychedelics like psilocybin and dissociatives like ketamine are excelling at facilitating fear extinction and neuroplasticity, thus promoting the resolution of the disease.

Importantly, some of the drugs mentioned in this paper function as a potentially powerful addition to psychotherapy. By opening a critical window of neuroplasticity and attenuating patient's response to traumatic memories, these substances enable the successful processing of traumatic memories that would otherwise remain inaccessible due to overwhelming autonomic arousal.

Although the results of recent trials are promising, the widespread integration of psychedelics into mainstream clinical practice is still something the patients will have to wait for. To overcome some of the problems, future research ought to prioritize large-scale, rigorously designed controlled trials, the standardization of therapeutic protocols, and a thorough adverse effects reporting. Ultimately, if these challenges can be resolved, psychedelic therapies hold the capacity to revolutionize trauma care, offering a causal treatment for PTSD.

8. Disclosure

8.1. Author Contribution

Conceptualization, Jakub Maksymilian Bajer and Aleksandra Włodarczyk; methodology, Krzysztof Maksym Kasparek and Grzegorz Kasparek; data curation, Hubert Kulawinek and Julia Obersztyn; formal analysis, Marta Czech and Adrianna Szczecińska; writing—original draft preparation, Jakub Maksymilian Bajer, Krzysztof Kasparek and Aleksandra Włodarczyk; writing—review and editing, Grzegorz Kasparek, Wiktoria Glanert and Aleksandra Mliczek; supervision, Piotr Mrozek. All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflicts of interest.

8.8. Declaration of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Gemini 3.1 Pro for the purpose of assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.

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