International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	PHARMACOLOGICAL TREATMENT OF PTSD WITH PSYCHEDELICS: A FUTURE OUTLOOK
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4392
RECEIVED	11 October 2025
ACCEPTED	19 December 2025
PUBLISHED	24 December 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

PHARMACOLOGICAL TREATMENT OF PTSD WITH PSYCHEDELICS: A FUTURE OUTLOOK

Michal Gorski *(Corresponding Author, Email: michal.gorski@stud.umed.lodz.pl)*
116th Military Hospital with Outpatient Clinic, Independent Public Health Care Institution, Opole, Poland
ORCID ID: 0009-0006-8762-2823

Adam Januszkiewicz
107th Military Hospital with Outpatient Clinic, Independent Public Health Care Institution, Wałcz, Poland
ORCID ID: 0009-0008-9488-2273

Wiktoria Januszkiewicz
107th Military Hospital with Outpatient Clinic, Independent Public Health Care Institution, Wałcz, Poland
ORCID ID: 0009-0005-5730-4333

Wojciech Machulski
Military Institute of Medicine, Warsaw, Poland
ORCID ID: 0009-0007-6337-5909

Martyna Ciarkowska
Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0001-4635-378X

Jan Makulski
1st Military Clinical Hospital with Outpatient Clinic, Lublin, Poland
ORCID ID: 0009-0006-7545-499X

Kamil Franczyk
10th Military Hospital with Outpatient Clinic, Independent Public Health Care Institution, Bydgoszcz, Poland
ORCID ID: 0009-0001-6294-5101

Karolina Swierk
Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0003-3784-9630

Damian Podkoscielny
Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0007-4979-1674

Maria Gierasimiuk
116th Military Hospital with Outpatient Clinic, Independent Public Health Care Institution, Opole, Poland
ORCID ID: 0009-0009-1450-9258

ABSTRACT

Globally, approximately 3.9% of the population is estimated to experience Post Traumatic Stress Disorder during their lifetime. PTSD is characterized as a complex mental health condition that develops following exposure to traumatic events, manifesting through intrusive thoughts, hyperarousal, and avoidance behaviors. Despite psychotherapy and conventional pharmacotherapy being the standard primary treatments, a significant number of individuals with PTSD continue to suffer from chronic symptoms and substantial psychiatric and medical comorbidities, underscoring a critical need for innovative therapeutic interventions.

A broad consensus in the literature indicates that existing PTSD treatments offer only marginal effectiveness for a considerable proportion of affected individuals. To address this, the present narrative review endeavors to synthesize the available knowledge regarding novel treatments for PTSD, specifically focusing on psychedelic drugs, acknowledging the current limitations in high-quality empirical literature on the subject.

The primary objective of this study is to conduct a narrative review on the efficacy of psychedelic therapy in managing PTSD. This involves examining current research and evaluating the benefits and drawbacks associated with various psychedelic interventions. The central clinical question explored is: For patients diagnosed with PTSD, what are the current and emerging psychedelic-based pharmacological treatments, and what is their prospective role in future clinical integration? It is anticipated that this study will provide valuable insights to both practitioners and patients regarding the potential utility of psychedelic compounds within the therapeutic landscape of PTSD.

KEYWORDS

PTSD, Psychedelics, MDMA, Ketamine, Psilocybin, Ibogaine, 5-Meo-DMT

CITATION

Michal Gorski, Adam Januszkiewicz, Wiktoria Januszkiewicz, Wojciech Machulski, Martyna Ciarkowska, Jan Makulski, Kamil Franczyk, Karolina Swierk, Damian Podkoscielny, Maria Gierasimiuk. (2025) Pharmacological Treatment of PTSD with Psychedelics: A Future Outlook. *International Journal of Innovative Technologies in Social Science*. 4(48). doi: 10.31435/ijitss.4(48).2025.4392

Introduction

Posttraumatic Stress Disorder is a severe and often chronic psychiatric condition that can emerge following direct or indirect exposure to actual or threatened death, serious injury, or sexual violence (First et al., 2022; Siddaway, 2024). The fifth edition, text revision, of the Diagnostic and Statistical Manual of Mental Disorders reclassifies PTSD within the category of 'trauma- and stressor-related disorders,' emphasizing its etiology rooted in traumatic exposure. For a diagnosis, symptoms must persist for at least one month and cause significant functional impairment.

PTSD is understood through various classifications and subtypes. The DSM-5-TR outlines four core symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, and marked alterations in arousal and reactivity (Du et al., 2022). Intrusion symptoms include distressing memories, nightmares, and flashbacks; avoidance involves evading trauma-related thoughts, feelings, or external reminders; negative alterations in cognitions and mood manifest as distorted beliefs, persistent negative emotional states, and feelings of detachment; and alterations in arousal and reactivity include irritability, hypervigilance, and sleep disturbances. The International Classification of Diseases, 11th version, also recognizes standard PTSD and additionally includes Complex PTSD, characterized by symptoms of dysregulation, negative self-concept, and difficulties in relationships, beyond the core PTSD symptoms (Fung et al., 2025).

"Flashbacks" are a hallmark symptom of PTSD, defined in DSM-5-TR and ICD-11 as the intrusive re-experiencing of traumatic events in the present. These distressing, sensory-based involuntary memories often occur uncontrollably while awake and can also manifest as nightmares during sleep. They can range from fleeting sensations of the traumatic experience re-occurring to a complete disconnection from current surroundings. Flashbacks are considered a unique symptom distinguishing PTSDs (Siddaway, 2025).

Traumatic events are common, with more than 70% of adults worldwide exposed at least once in their lifetime, and approximately 10% developing PTSD (Du et al., 2022). A multitude of risk factors contribute to its development, including pre-trauma, peri-trauma, and post-trauma factors (Jones et al., 2024; Jowf et al., 2022). These include experiences such as sexual violence, where over half of women experiencing it develop PTSD (Li et al., 2023). War-related trauma significantly increases risk, with recent studies showing PTSD prevalence rates up to 22% among military personnel (Tedla et al., 2024). Refugee status is a substantial risk factor, with systematic reviews demonstrating elevated PTSD rates due to cumulative traumas like war, persecution, and loss (Andualem et al., 2024; Bryant et al., 2023; Handiso et al., 2023; Lechner-Meichsner et al., 2024; Nowak et al., 2023; Patanè et al., 2022). Personal losses, such as the unexpected death of a loved one, are also significant risk factors for PTSD, especially sudden or violent losses (Rheingold et al., 2024; Wild et al., 2023). Life-threatening severe medical illnesses and critical care events are recognized triggers for PTSD, with survivors of intensive care units frequently experiencing symptoms (Carlson et al., 2023; Lunkenheimer et al., 2023). Complications during pregnancy or childbirth, including obstetric interventions, obstetric violence, previous mental illness, and poor social support, can also precipitate postpartum PTSD (Khsim et al., 2022; Nguyen et al., 2022). Natural disasters are potent traumatic stressors, often resulting in PTSD (Golitaleb et al., 2022). Genetic factors also play a role, with studies indicating heritable components influence vulnerability and risk (Nievergelt et al., 2023).

Globally, the prevalence of PTSD varies significantly, with a lifetime prevalence estimated at 3.9% and annual prevalence up to 3.5% in US adults (Koenen et al., 2017). An umbrella review of PTSD prevalence indicates a wide range from 2.5% to 74%, depending on assessment methods and trauma nature (Schincariol et al., 2024). Higher rates are often observed in post-conflict settings (Fung et al., 2025). There are also notable sex differences, with women generally having a higher risk of developing PTSD and exhibiting different vulnerabilities to specific risk factors compared to men (Schincariol et al., 2024). Social disadvantages, including younger age, female sex, being unmarried, lower education, and lower household income, are associated with an increased risk of lifetime PTSD among trauma-exposed individuals (Koenen et al., 2017).

The economic burden of PTSD is substantial for both individuals and society. In the United States, the total excess cost of PTSD in 2018 was estimated to be considerable, driven by direct healthcare costs and indirect costs such as unemployment. For military populations, the burden is heavily influenced by disability and direct healthcare costs (Davis et al., 2022). These costs rival those of other major mental health conditions, with a higher economic burden observed in patients with PTSD and mental health comorbidities (Davis et al., 2022; Stanicic et al., 2024; Vliet et al., 2024).

Comorbidity is the norm for PTSD, with frequent occurrence in affected cases. Over 80% of individuals with PTSD in the general population experience at least one additional lifetime mental health disorder, and around 50% experience three or more (Qassem et al., 2020; Sbisa et al., 2024). Major depression is the most common co-occurring condition, with its frequency increasing with PTSD symptom severity. Other frequent psychiatric comorbidities include various anxiety disorders and substance use disorders (Qassem et al., 2020). Physical health conditions frequently associated with PTSD span multiple systems, including metabolic, circulatory, and musculoskeletal diseases (Ferretti et al., 2019; Lunkenheimer et al., 2023). Autoimmune diseases are also increasingly recognized as comorbidities (Mandagere et al., 2025). These physical health consequences may lead to increased healthcare utilization and premature death (Moder et al., 2025).

Pathophysiology

The neurobiological underpinnings of post-traumatic stress disorder are characterized by a complex interplay of genetic predispositions, epigenetic modifications, and environmental factors (Ressler et al., 2022; Seah et al., 2025). These interactions contribute to observable alterations in brain structure and function, particularly within neural circuits vital for fear processing, emotional regulation, and memory consolidation. Recent advancements in neuroimaging and molecular research have deepened the understanding of these mechanisms (Hinojosa et al., 2024). Proposed theories of PTSD pathophysiology often center on dysregulation within a fear learning and memory network, prominently involving the amygdala, hippocampus, and prefrontal cortex (Harnett et al., 2020; Ressler et al., 2022). The amygdala plays a critical role in the acquisition and expression of fear, while the hippocampus is crucial for contextual processing and the extinction of fear memories (Ressler et al., 2022). Dysfunction in the medial prefrontal cortex, which normally inhibits threat-related memories and behaviors, is also frequently observed (Iqbal et al., 2023; Ressler et al., 2022).

Furthermore, alterations in neurotransmitter systems and the hypothalamic-pituitary-adrenal axis are key components of PTSD's pathophysiology (Iqbal et al., 2023; Sbisa et al., 2024). The noradrenergic system,

for instance, is implicated in enhanced encoding of emotional memories and hyperarousal; similarly, imbalances in other neurotransmitters such as serotonin, glutamate/GABA, and dopamine, alongside neuropeptides like corticotropin-releasing factor and the opioid system, contribute to the stress response and fear conditioning deficits observed in PTSD (Charney, 1993; Iqbal et al., 2023; Tedesco et al., 2021; Torres-Berrío & Nava-Mesa, 2018). Cognitively, PTSD is associated with impaired control over emotional cues, manifesting as re-experiencing symptoms, and deficits in processing speed, verbal learning, memory, attention, and working memory (Hayes et al., 2012; Sep et al., 2021; Suliman et al., 2025). This is further compounded by theories suggesting that trauma memories are often fragmented, sensory-based, and involuntarily triggered, which contributes to a persistent sense of threat and negative appraisals of the event and its consequences (Chiu et al., 2023).

Chronic overactivation of the sympathoadrenal medullary system and the hypothalamic-pituitary-adrenocortical axis, induced by ongoing stress, perpetuates this heightened arousal, thereby contributing to PTSD progression (Azevedo et al., 2024). These physiological changes can culminate in structural brain alterations, including decreased volumes in cortical areas such as the prefrontal cortex and anterior cingulate cortex, along with white matter tract abnormalities and gray matter changes in the hippocampus and basolateral amygdala (Bird et al., 2021; Iqbal et al., 2023).

Methodology

The methodological approach employed in this article encompassed the synthesis of evidence derived from randomized controlled trials, observational studies, and meta-analyses. A comprehensive literature review was conducted utilizing databases such as PubMed and Google Scholar, supplemented, in specific cases, by direct correspondence with authors. This work integrates data from a diverse array of research to offer a holistic perspective on pharmacological treatments for PTSD involving psychedelics, emphasizing their hypothesized mechanisms of action and demonstrated clinical efficacy.

Psilocybin

Psilocybin is a naturally occurring tryptamine alkaloid, chemically identified as 4-phosphoryloxy—dimethyltryptamine (Glatfelter et al., 2022). It functions as a serotonergic psychedelic and a prodrug, converting into its psychoactive metabolite, psilocin (4-hydroxy—dimethyltryptamine), upon ingestion (Irizarry et al., 2022). This compound was first isolated in 1957 by Albert Hofmann. (Hofmann et al., 1958) Psilocybin is found in various species of "magic mushrooms," predominantly within the Psilocybe genus, but also in Panaeolus, Pluteus, and Gymnopilus species, with natural habitats spanning regions like South America, Mexico, and subtropical areas of the United States (Court et al., 2022; Strauss et al., 2022). The most common route of administration for psilocybin is oral ingestion (Straumann et al., 2024). For research and therapeutic applications, pure psilocybin can be extracted from these fungi using methods such as methanolic extraction or microwave-assisted extraction (Polo-Castellano et al., 2022). Additionally, kilogram-scale chemical synthesis methods have been developed to ensure consistent yield and purity of the compound (Kargbo et al., 2020). This allows for rigorous control over dosage and minimizes the variability often associated with other naturally derived substances, which is critical for clinical trials investigating its efficacy in conditions like PTSD (Choi et al., 2024).

Mechanism of action

Psilocybin and its active metabolite, psilocin, exert their psychotropic effects primarily through agonism at serotonin 5-HT2A receptors, particularly those located in cortical regions. This interaction is thought to modulate glutamatergic neurotransmission, leading to altered functional connectivity within brain networks such as the default mode network, and is attributed to anxiolytic, antidepressant and halucinogenic properties of psilocybin. (Choi et al., 2024). This agonism also extends to various other serotonin receptor subtypes, although their precise contributions to psilocin's therapeutic effects remain less characterized (Dodd et al., 2022). Specifically, psilocin acts as a partial agonist at 5-HT1A, 5-HT1D, 5-HT1E, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5A, 5-HT6, and 5-HT7 receptors, and as a full agonist at 5-HT1B and 5-HT1F receptors, albeit with varying affinities. The high affinity for the 5-HT2A receptor subtype is particularly responsible for the psychotropic effects of psilocin, especially within the amygdala, thalamus, and prefrontal cortex (Yerubandi et al., 2024).

Efficacy

Emerging clinical research indicates a growing interest in the efficacy of psilocybin for Post-Traumatic Stress Disorder treatment, particularly reflected in recent studies. A Phase 2, open-label trial published in 2025, investigating single-dose COMP360 psilocybin in individuals with PTSD, reported a clinically meaningful reduction in PTSD symptom severity as measured by the CAPS-5 total score. This improvement demonstrated a rapid onset, observed the day after treatment, and was sustained throughout the trial period. Encouragingly, over 75% of participants were classified as responders, and over half achieved remission by the 12-week mark, a result that compares favorably to the approximately 60% response rates typically seen with SSRI treatments for PTSD. This study is considered a foundational clinical trial for psilocybin in PTSD, being the first to specifically report on its safety and tolerability in this patient group (McGowan et al., 2025). While large-scale randomized controlled trials specifically for psilocybin and PTSD were not widely published as of 2021, ongoing clinical trials suggest a rapidly evolving research landscape. Beyond direct PTSD symptom reduction, psilocybin has shown evidence in preclinical and other clinical settings for its ability to reduce depressive symptoms and anxiety, and enhance fear memory extinction, all of which are relevant to the complex symptomatology of PTSD (Miller & Zoladz, 2025). A meta-analysis from 2022 indicated that psilocybin treatment, even in microdosing regimens, can lead to overall improvement in psychiatric illnesses including PTSD, with effects potentially lasting four to eight weeks after two sessions and a noted correlation between decreased amygdala blood flow and reduced depressive symptoms (Irizarry et al., 2022). This body of work underscores the therapeutic potential of psilocybin as a novel intervention for PTSD. (Irizarry et al., 2022; McGowan et al., 2025; Miller & Zoladz, 2025)

Quality of Life and Patient Satisfaction

Clinical research indicates that psilocybin treatment for Posttraumatic Stress Disorder may lead to notable improvements in patient well-being and quality of life. A Phase 2 open-label clinical trial investigating single-dose psilocybin for PTSD reported consistent and durable pre-post treatment improvements in quality of life, as measured by the EQ-5D-5L index score, and reductions in functional impairment. This trial also observed rapid and sustained improvements in patient-rated PTSD symptom severity (McGowan et al., 2025). Beyond PTSD-specific outcomes, systematic reviews of randomized controlled trials involving psilocybin for various psychiatric conditions have shown an enhanced sense of well-being, life satisfaction, and positive mood that can last up to six months post-treatment, often alongside psychotherapy (IsHak et al., 2023). Patients have described their psilocybin experiences as profoundly meaningful, suggesting a high degree of satisfaction with the treatment and reporting increased positive attitudes, mood, social effects, and behavior, with no adverse effects reported at 14-month follow-up in one study (Daniel & Haberman, 2017). However, further qualitative research specifically exploring patient experiences and satisfaction with psilocybin-assisted therapy for PTSD is still an area needing more focused investigation (Schuitmaker, 2023).

Adverse Events

While the therapeutic potential of psilocybin for PTSD is promising, a comprehensive understanding of its safety profile and potential adverse events is crucial for widespread clinical adoption (Omidian & Omidian, 2025). A study on the safety and tolerability of a single dose of COMP360 psilocybin in individuals with PTSD reported no serious adverse events or withdrawals over a 12-week period. The most frequently reported adverse events were mild or moderate, including headaches, nausea, and fatigue. A further 70 treatment-emergent adverse events were noted on the administration day, with 64 of these resolving by the following day, underscoring the transient nature of most acute reactions. Other commonly observed adverse events, consistent with prior psilocybin research, encompassed hallucinations, paresthesia, and alterations in mood and euphoria, typically resolving quickly (McGowan et al., 2025).

Despite the generally favorable safety profile observed in controlled clinical settings, with adverse events typically mild and transient and no reported psilocybin-induced psychosis or Hallucinogen Persisting Perception Disorder (Kaminski & Reinert, 2023; McGowan et al., n.d.), specific concerns regarding suicidality require careful consideration. The meta-analysis by Roméo et al. (Roméo et al., 2024) reported no suicide attempts during the acute phase among over 1000 administrations, though three participants engaged in self-harm in the post-acute phase. This general safety is balanced by individual case reports, such as that by Wahba et al. (Wahba et al., 2024), detailing a participant experiencing worsening suicidal ideation and prolonged adverse events following psilocybin administration, even within a clinical setting. Furthermore, a Phase 2 trial for PTSD noted suicidal ideation in two participants (McGowan et al., 2025). These findings underscore that

while psilocybin is generally well-tolerated under supervision, rigorous patient selection, intensive clinical vigilance, and robust therapeutic support are essential to manage the potential for such adverse psychological reactions, particularly when dealing with complex mental health conditions like PTSD.

How it differs from other psychadelics used in treatment of PTSD?

While other psychedelic compounds like MDMA have shown considerable promise for PTSD treatment, psilocybin distinguishes itself through its serotonin 5-HT2A receptor agonism, which is believed to mediate its consciousness-altering and therapeutic effects, potentially offering a distinct neurobiological pathway for symptom amelioration compared to the empathogenic actions of MDMA (Choi et al., 2024; Sottile & Vida, 2022). Psilocybin primarily affects emotional modulation, neurotransmitters, and neuroplasticity, reducing amygdala reactivity to negative stimuli and impacting threat response (Choi et al., 2024). In contrast, MDMA acts primarily through the inhibition of monoamine reuptake, particularly serotonin, leading to an acute surge of extracellular monoamines and fostering a state of heightened trust, empathy, and self-compassion, which are key to its "entactogenic" properties (Bird et al., 2021; Sottile & Vida, 2022; Wolfgang et al., 2025).

This difference in pharmacological mechanisms may translate into distinct therapeutic profiles. Studies suggest that psilocybin's psychological effects can be more variable and less predictable compared to MDMA, which tends to produce a more stable pattern of effects (Krediet et al., 2020). Furthermore, psilocybin's affect-intensifying effects, including the potential to amplify anxiety when re-experiencing traumatic memories, may be more challenging for some PTSD patients (Krediet et al., 2020). Both compounds have received significant attention, with MDMA-assisted therapy receiving "Breakthrough Therapy" designation for PTSD, and psilocybin for resistant depression (Bird et al., 2021; Sarparast et al., 2022). These nuanced pharmacological differences underscore the critical need for tailoring psychedelic-assisted psychotherapy to individual patient needs and optimizing treatment outcomes for this complex disorder. Some research even explores the potential benefits of combining these therapies, such as MDMA-assisted therapy followed by psilocybin-assisted therapy (Bird et al., 2021).

Ketamine

Ketamine is a synthetic arylcyclohexylamine derivative, chemically related to phencyclidine, that was developed in 1962 by Calvin Stevens of the pharmaceutical laboratory Parke-Davis and was first administered to humans in 1964 as a less hallucinogenic and shorter-acting anesthetic agent (Hirota & Lambert, 2022). Ketamine primarily acts as a non-competitive antagonist of the N-methyl-D-aspartate receptor, a crucial excitatory neurotransmitter receptor in the brain (Bell & Kalso, 2018). This action is fundamental to its diverse pharmacological effects. As a dissociative anesthetic, ketamine induces a trance-like state characterized by profound analgesia, sedation, and amnesia, where sensory inputs may reach cortical areas but are not fully processed in association areas, distinguishing it from traditional anesthetics (Mion & Villevieille, 2013). Beyond its traditional role in inducing dissociative sedation and analgesia, ketamine's applications have broadened considerably due to its multifaceted pharmacological properties. It is now recognized for its use in pain management—including acute, chronic, and cancer-related pain—and as a rapid-acting antidepressant for various neuropsychiatric disorders, such as treatment-resistant depression, bipolar disorder, anxiety spectrum disorders, and substance use disorders (Gibuła-Tarłowska et al., 2025; Johnston et al., 2023). Its antidepressant effects are notably rapid, often manifesting within hours or days rather than weeks or months (Johnston et al., 2023). Ketamine can be administered via multiple routes, such as intramuscular, intravenous, and intranasal methods, with intranasal esketamine having received approval for the treatment of resistant depression (Fuller et al., 2024; Swainson et al., 2022; Tran & MacDougall, 2024).

Mechanism of Action

Primary mechanism of action of ketamine involves non-competitive antagonism of the N-methyl-D-aspartate receptor, a key excitatory neurotransmitter receptor in the brain (Bell & Kalso, 2018). However, its pharmacological profile is considerably more intricate, involving modulation of -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, mammalian target of rapamycin (mTOR) signaling, and brain-derived neurotrophic factor (Askariyan et al., 2025; Day & Agrawal, 2025).

For PTSD patients, ketamine's mechanisms are thought to contribute to the restoration of synaptic connectivity and an increase in neuronal plasticity, particularly at low doses (Day & Agrawal, 2025). This is crucial as PTSD has been conceptualized as a "synaptic disconnection syndrome" (Krediet et al., 2020; Mohamed et al., 2022). Ketamine/'s blockade of extra-synaptic NMDA receptors leads to changes in

intracellular signaling pathways that increase BDNF and AMPA signaling, promoting synaptogenesis and synaptic spine maturation, which are vital for brain plasticity (Almeida et al., 2024; Day & Agrawal, 2025). Furthermore, ketamine has shown effects in reducing traumatic memories and fear by acting on synaptic pathways in key brain regions involved in fear processing, such as the hippocampus, amygdala, and prefrontal cortex (Almeida et al., 2024). Its impact on glutamate signaling is essential for memory processes like reconsolidation and extinction learning, which are often impaired in PTSD (Krediet et al., 2020). Additionally, ketamine modulates dopaminergic neurocircuits and has been found to "silence" excessive NMDA receptor-dependent burst firing in the lateral habenula, often referred to as the "anti-reward center" of the brain, which is implicated in depressive symptomatology and negative experiences (Wang et al., 2025).

Efficiacy

Clinical studies have demonstrated that ketamine can lead to rapid and robust reductions in PTSD symptoms, including intrusive thoughts, avoidance behaviors, hyperarousal, and heightened anxiety. These effects are often observed within hours and can persist for several weeks, specifically up to 28 days (Beaglehole et al., 2025; Wang et al., 2025). A systematic review and meta-analysis confirmed that ketamine significantly reduced Clinician-Administered PTSD scores, PTSD Checklist scores, and Montgomery-Asberg Depression Rating scores, with benefits noted as early as day one and lasting up to four weeks (Sicignano et al., 2024). This rapid onset of action and sustained efficacy differentiate ketamine from conventional pharmacological interventions for PTSD, such as selective serotonin reuptake inhibitors, which typically require prolonged treatment durations to manifest therapeutic benefits (Wang et al., 2025). Ketamine has also been shown to be more efficacious than fentanyl for PTSD (Beaglehole et al., 2025). While some research suggests limited effectiveness of ketamine as a standalone treatment, its potential as a targeted adjunct to trauma-focused psychotherapy is highlighted (Topel & Ciccone, 2025).

Quality of Life and Patient Satisfaction

Ketamine treatment for Posttraumatic Stress Disorder has demonstrated promising effects on patient well-being, indirectly suggesting improvements in quality of life and patient satisfaction, primarily through significant reductions in core PTSD and comorbid depressive symptoms. Clinical trials have revealed that ketamine can substantially reduce Impact of Events Scale – Revised ratings, with its beneficial effects lasting up to a week (Beaglehole et al., 2025). Furthermore, ketamine-assisted psychotherapy has been noted to help patients passively process unpleasant memories, leading to more durable improvements in PTSD symptoms compared to placebo (Mohamed et al., 2022). Long-term treatment with ketamine has also been associated with reduced hospitalization rates for severe comorbid conditions like PTSD and treatment-resistant depression, further supporting its positive impact on patient outcomes and overall quality of life (Almeida et al., 2024).

Adverse events

Ketamine therapy for PTSD is associated with a range of adverse events, which are generally well-documented across clinical studies. Frequently reported side effects include drowsiness, nausea, dizziness, altered vision, and altered perception (Krediet et al., 2020; Mohamed et al., 2022). Dose-dependent dissociative symptoms are also commonly observed (Krediet et al., 2020; Mohamed et al., 2022). In some instances, ketamine can induce transient anxiety, though supportive clinical settings can help minimize such reactions (Krediet et al., 2020; Mohamed et al., 2022). Ketamine exhibits sympathomimetic effects, leading to an increase in heart rate and blood pressure, making severe cardiovascular pathologies and certain forms of hypertension contraindications for its use (Krediet et al., 2020; Mohamed et al., 2022).

A systematic review and meta-analysis of ketamine for PTSD highlighted that dose-related dissociative and psychomimetic symptoms generally peaked around 40 minutes post-infusion and subsided to baseline levels within two hours. Notably, this review observed no psychotic or manic symptoms during treatment, nor was ketamine exposure linked to an exacerbation of PTSD-related symptoms (Almeida et al., 2024). Another review suggests that the adverse effects of ketamine are most pronounced with the initial infusion and tend to lessen with subsequent treatments, often resolving entirely within a day after the infusions (Sicignano et al., 2024). While ketamine is associated with short-term dissociative and cardiovascular effects (Beaglehole et al., 2025), these findings collectively suggest that, with proper patient selection and monitoring in a controlled clinical environment, the adverse events associated with ketamine treatment for PTSD are generally transient and manageable. However, the long-term safety profile, particularly concerning repeated administration and potential for abuse or neurocognitive sequelae, necessitates further rigorous investigation through extended clinical trials (Krediet et al., 2020).

How it differs from other psychadelics used in treatment of PTSD?

Ketamine's mechanism of action, primarily as an NMDA receptor antagonist, distinguishes it from classic serotonergic psychedelics such as psilocybin and MDMA, which primarily agonize 5-HT2A receptors, thereby offering a distinct neuropharmacological approach to PTSD treatment. This difference translates into variations in subjective experience and therapeutic strategies, with ketamine often facilitating rapid symptomatic relief and neuroplastic changes, while serotonergic psychedelics are thought to promote deeper emotional processing and insight (Wang et al., 2025). For instance, ketamine's dissociative properties may allow for a detachment from traumatic memories, facilitating their processing, whereas MDMA-assisted psychotherapy aims to foster empathy and reduce fear to re-engage with traumatic narratives in a supported setting. Unlike classic psychedelics that often require extended integration periods, ketamine's therapeutic effects manifest rapidly, though its sustained efficacy typically necessitates repeated administrations or integration within a psychotherapeutic framework for longer-term benefits (Abdallah et al., 2022; Krediet et al., 2020). Ultimately, while diverse psychoactive substances offer varied approaches to PTSD, ketamine stands out for its rapid neurobiological actions, dissociative properties, and distinct therapeutic trajectory, requiring careful consideration of its unique administration and integration needs for sustained patient benefit. However, key concerns about ketamine therapy, such as dissociative symptoms, hemodynamic instability, and the potential for abuse with long-term use, underscore the ongoing need for research into its long-term effects and the development of alternative agents with similar efficacy but fewer adverse reactions (Reddy et al., 2024).

MDMA (Midomafetamine)

3,4-methylenedioxymethamphetamine, widely recognized by its street names "ecstasy" or "molly," is a derivative of methamphetamine, classified as a psychostimulant (Meyer, 2013). It was initially synthesized in 1912 by Merck chemist Anton Köllisch, who marketed it as an "anorectic" under the designations "Methylsafrylamin" and "Safrylmethylamin" (Freudenmann et al., 2006). It is broadly categorized as an entactogen, owing to its pronounced empathogenic properties in human subjects (Stocker & Liechti, 2024; Straumann et al., 2025). Despite Merck not advancing its development beyond a chemical precursor stage, its distinctive psychoactive properties were independently rediscovered by Alexander Shulgin in the 1970s. During the late 1970s and early 1980s, MDMA began to be utilized by various psychotherapists as an adjunct to talk therapy (Benzenhöfer & Passie, 2010; Passie, 2018). Initial open-label pilot investigations, particularly those conducted by Greer and Tolbert, documented significant and enduring enhancements in mood, social functionality, and self-insight subsequent to a single MDMA-assisted therapeutic session (Greer & Tolbert, 1986, 1990, 1998). However, MDMA regained prominence in research for its potential in treating post-traumatic stress disorder, with recent Phase 3 trials confirming its safety and efficacy as a breakthrough therapy (Mitchell et al., 2021).

Mechanism of Action

MDMA primarily functions by promoting the release of serotonin, dopamine, and norepinephrine within the mesolimbocortical circuitry of the brain, achieving this by reversing membrane-bound transporters and inhibiting their reuptake. Specifically, MDMA acts as a weak agonist on 5-HT1 and 5-HT2 serotonin receptors, targeting 5-HT2A, 5-HT2B, and 5-HT2C receptors, which significantly influence neural activity, perception, cognition, and mood (Tedesco et al., 2021). The substantial release of serotonin contributes to a bilateral reduction in amygdala activity, a brain structure critically involved in the acquisition and storage of fearful memories. This reduction, coupled with increased activation of the serotonergic system, leads to altered emotional and cognitive processes, including enhanced cognitive flexibility and a diminished response to negative stimuli (Varker et al., 2021). Beyond its impact on the serotonergic system, MDMA also binds directly at the alpha-2 adrenergic, beta-1 adrenergic, and D1 and D2 dopaminergic receptors (Lewis & Byrne, 2023).

Concurrently, MDMA indirectly elevates levels of neurohormones such as oxytocin and cortisol (Tedesco et al., 2021). The increase in oxytocin is induced by MDMA-stimulated 5-HT efflux or through direct affinity to 5-HT receptors, and by its action on the serotonin transporter and 5-HT4 receptors on oxytocin neurons. This surge in oxytocin is hypothesized to contribute to enhanced feelings of trust, empathy, and prosocial behaviors (Lewis & Byrne, 2023). Oxytocin also modulates neural circuitry related to the neurobiological response to trauma, including the amygdala and prefrontal cortex, and can reduce amygdala activity (Feduccia et al., 2017). Furthermore, MDMA influences the hypothalamic-pituitary-adrenal axis, leading to increased cortisol levels. MDMA also modulates glutamatergic neurotransmission, which is part of the array of abnormal chemical regulations found in brain circuits of PTSD patients that are affected by MDMA (Tedesco et al., 2021).

Efficiency

Clinical investigations have demonstrated that MDMA-assisted psychotherapy effectively mitigates PTSD symptoms, leading to sustained therapeutic benefits and improved functional outcomes in individuals with severe PTSD (Mitchell et al., 2023). Recent data from multiple Phase 3 multicenter clinical trials underscore this efficacy. For instance, the first Phase 3 study, published in 2021, and a second subsequent study, both identified in recent reviews, demonstrated significant reductions in PTSD symptom severity, higher response and remission rates, and a greater proportion of participants who no longer met criteria for a PTSD diagnosis compared with those who received placebo (Lewis & Byrne, 2023; Sippel et al., 2024). Across these trials, 67%–71% of individuals receiving MDMA-assisted therapy lost their PTSD diagnosis, compared to 32%–48% in placebo-assisted therapy groups (Wolfgang et al., 2025).

The therapeutic potential of MDMA-assisted psychotherapy has led the Food and Drug Administration to designate it as a "Breakthrough Therapy" for PTSD in 2017, a status reaffirmed in recent literature, which facilitates an accelerated review process (Sippel et al., 2024; Wolfgang et al., 2025). While the initial New Drug Application faced a rejection in 2024, the FDA is requiring an additional Phase 3 trial to further evaluate this treatment, indicating ongoing rigorous assessment (Wolfgang et al., 2025).

The development of structured protocols is central to MDMA-assisted psychotherapy. Typical treatment involves a robust psychotherapeutic protocol, often spanning approximately 40 hours of therapist time, delivered by a male-female co-therapist dyad (Lewis & Byrne, 2023). These protocols generally comprise three to four initial preparatory psychotherapy sessions, followed by two to three full-day MDMA-assisted sessions, each succeeded by three to four integration psychotherapy sessions (Colcott et al., 2024). To ensure fidelity and effectiveness of these treatments, comprehensive therapy training programs have been developed, consisting of in-person training, role-playing, video-recorded MDMA sessions, e-learning modules, and readings (Lewis & Byrne, 2023). Reflecting growing confidence in this therapeutic approach, Australia made a significant regulatory decision in 2024, becoming the first country to schedule MDMA for medicinal use for PTSD, allowing authorized psychiatrists to prescribe it (Colcott et al., 2024).|

Quality of Life and Patient Satisfaction

Beyond symptomatic relief, MDMA-assisted psychotherapy has demonstrated a notable impact on patients' quality of life and overall satisfaction with their treatment outcomes. Improvements extend beyond core PTSD symptoms to broader measures of well-being, social functioning, and a reduction in functional impairment (Sippel et al., 2024). Participants frequently report enhanced self-compassion, greater emotional regulation, and improved interpersonal relationships, contributing to a more holistic recovery (Tedesco et al., 2021). This comprehensive improvement in psychological and social domains underscores the potential for MDMA-assisted psychotherapy to foster profound and lasting changes that extend beyond symptom reduction, thereby enriching patients' overall life satisfaction (Sippel et al., 2024).

Adverse events

While MDMA-assisted therapy demonstrates significant efficacy and improvements in quality of life for PTSD patients, a thorough examination of its safety profile and potential adverse events is crucial for comprehensive clinical understanding (Sippel et al., 2024). Despite the generally favorable safety profile observed in clinical trials, ethical considerations surrounding therapist-patient boundaries, particularly during states of enhanced suggestibility induced by MDMA, warrant careful attention and robust oversight mechanisms to mitigate potential risks (Lewis & Byrne, 2023). Considering somatic reactions, common acute physiological effects reported during MDMA administration include transient increases in blood pressure, heart rate, and body temperature (Smith et al., 2021). Therefore, it cannot be applied to individuals with pre-existing cardiovascular conditions or other medical contraindications without stringent medical supervision and careful risk assessment (Lewis & Byrne, 2023).

How it differs from other psychadelics used in treatment of PTSD?

While other psychedelic compounds like psilocybin and ayahuasca are also being explored for their therapeutic potential in PTSD, MDMA’s unique pharmacological profile, particularly its prosocial and empathogenic effects, distinguishes its mechanism of action and clinical utility from these other substances in the context of psychotherapy (Tedesco et al., 2021). Specifically, MDMA’s capacity to foster an enhanced therapeutic alliance (Zeifman et al., 2024) and reduce defensiveness during therapy sessions appears to be a critical mediator of its positive outcomes, contributing to increased openness to experience (Sippel et al., 2024).

This differentiates its mode of action from classical psychedelics (Tedesco et al., 2021). However, this differentiation is not absolute, as classical psychedelics like psilocybin have also been shown to increase emotional empathy (Irizarry et al., 2022) as well as foster insightfulness and openness (often observed through divergent thinking) (Irizarry et al., 2022)—factors critical for effective psychotherapy in PTSD (Zeifman et al., 2024). The capacity of various psychedelic substances to enhance engagement with psychotherapeutic interventions through similar psychological and neurobiological effects, including diminished fear (Bird et al., 2021) and increased insightfulness (Irizarry et al., 2022), suggests that the "unique" mechanism attributed to MDMA's prosocial effects might be a shared feature across the broader class of psychedelics that facilitate therapeutic processes.

5-MeO-DMT (Mebufotenin)

5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is a naturally occurring psychedelic tryptamine found in various plant and animal species, notably in the secretions of the Bufo alvarius toad, and has been historically utilized in indigenous rituals (Ermakova et al., 2021; Reckweg et al., 2021; Uthaug et al., 2019). While sharing chemical similarities with N,N-dimethyltryptamine (N,N-DMT), 5-MeO-DMT elicits distinct subjective experiences (Lawrence et al., 2022; Stavely, 2025). Its pharmacological action primarily involves agonism at serotonin receptors, particularly the 5-HT1A and 5-HT2A subtypes, with a notable higher affinity for the 5-HT1A receptor, which may contribute to its unique psychoactive profile (Jefferson et al., 2023; Nogueira et al., 2023; Reckweg et al., 2022). Moreover, studies indicate that 5-MeO-DMT modulates other neurotransmitter systems, including dopamine, glutamate, and GABA, suggesting multifaceted neurobiological effects (Stavely, 2025).

Mechanism of Action

Multifaceted interactions with various neurotransmitter systems underpin the compound's rapid onset and profound, often ineffable, subjective effects (Stavely, 2025). Unlike classical psychedelics such as psilocybin, which primarily agonize the 5-HT2A receptor to exert anxiolytic, antidepressant, and hallucinogenic effects (Choi et al., 2024), 5-MeO-DMT's potent agonism at 5-HT1A receptors is hypothesized to mediate its rapid onset and ego-dissolving properties (Jefferson et al., 2023; Reckweg et al., 2022). This differential affinity is significant, as the 5-HT1A receptor is abundant in brain regions governing anxiety, mood, and emotions, and its stimulation typically produces inhibitory effects that can lead to anxiolysis (Nogueira et al., 2023).

This unique pharmacological profile suggests several mechanisms that could be particularly beneficial for treating Post-Traumatic Stress Disorder. The rapid induction of profound ego dissolution and mystical-type experiences by 5-MeO-DMT is thought to facilitate the re-processing and transformation of traumatic material, contributing to significant improvements in PTSD symptomatology observed in observational studies and case reports (Davis et al., 2020; Ragnhildstveit et al., 2023). This capacity for an immediate, profound shift in perspective may enable individuals to view their trauma in a different, less threatening way (Ragnhildstveit et al., 2023). Furthermore, 5-MeO-DMT, similar to other psychedelics, demonstrates potential for promoting neuroplasticity, including neurogenesis, spinogenesis, and synaptogenesis, which can underpin rapid antidepressant and anxiolytic effects and facilitate fear extinction—a crucial process in overcoming trauma. It may also decrease amygdala reactivity during emotional processing, which is particularly relevant given the heightened amygdala activity often seen in PTSD patients (Krediet et al., 2020). Additionally, some research suggests 5-MeO-DMT possesses neuroprotective, regenerative, and anti-inflammatory properties that might address the underlying etiology of cognitive impairment and PTSD (Davis et al., 2020). The phenomenon of "reactivations," where elements of the acute experience may spontaneously re-emerge, is also considered a potential contributor to the sustained long-term therapeutic benefits observed (Turkia, 2024). These combined actions, particularly its strong 5-HT1A agonism, ego-dissolving effects, and neuroplastic changes, highlight 5-MeO-DMT's distinct and promising therapeutic avenues for PTSD treatment.

Efficiency

Emerging research indicates that 5-MeO-DMT shows considerable promise in alleviating symptoms of PTSD, anxiety, and depression. Observational studies and case reports have demonstrated significant and substantial reductions in PTSD, depression, anxiety, suicidal ideation, and cognitive impairment, often following a single administration (Davis et al., 2020; Ragnhildstveit et al., 2023). Notably, improvements in PTSD have been sustained for up to 12 months post-treatment in some cases (Ragnhildstveit et al., 2023). A clinical study investigating 5-MeO-DMT for treatment-resistant depression reported a rapid antidepressant

effect, with significant symptom reduction and a high rate of remission within one week (Wojtas, 2023). These therapeutic benefits are often associated with profound mystical-type experiences and ego dissolution facilitated by 5-MeO-DMT (Davis et al., 2020; Ragnhildstveit et al., 2023). While a paucity of evidence exists, particularly for trauma- and stress-related psychopathology (Ragnhildstveit et al., 2023), 5-MeO-DMT is also being explored for conditions such as bipolar disorder and post-partum depression (Wojtas, 2023), and its safety and tolerability in sub-psychedelic doses for moderate anxiety and depression are currently under investigation in clinical trials (Millón et al., 2025).

Quality of Life and Patient Satisfaction

Beyond symptom reduction, 5-MeO-DMT has been linked to enhanced psychological flexibility, improved overall life satisfaction, and heightened mindfulness-related capacities (Davis et al., 2020). Recent research further elucidates these benefits. Psychological flexibility, defined as the ability to fully engage with the present moment and adapt behavior to serve valued ends (Krabbe et al., 2024), has been shown to increase following 5-MeO-DMT administration (Ragnhildstveit et al., 2023). This increase is strongly associated with significant reductions in symptoms of PTSD, depression, and anxiety (Davis et al., 2020; Ragnhildstveit et al., 2023). 5-MeO-DMT is thought to enhance psychological flexibility by fostering profound insights into personal values and challenging pre-existing beliefs, thereby promoting adaptability and open-mindedness (Holas & Kamińska, 2023).

Moreover, patients report substantial improvements across various domains related to personal well-being and quality of life. Positive changes have been noted in individuals' sense of personal well-being or life satisfaction (77%), life's purpose (75%), life's meaning (73%), social relationships (73%), attitudes about life (74%), attitudes about self (72%), mood (59%), behavior (63%), attitudes about death (56%), spirituality (65%), relationship to nature (57%), and their perspectives on the true nature of reality and the universe (69%) (Davis et al., 2020). These findings are supported by studies indicating that a single administration of 5-MeO-DMT is associated with increased life satisfaction and heightened mindfulness-related capacities (Davis et al., 2020; Ragnhildstveit et al., 2023). The integration of mindfulness skills with psychedelic insights shows promise for sustaining psychological flexibility, facilitating balanced responses to internal and external stimuli, and promoting adaptive coping mechanisms for life's challenges (Holas & Kamińska, 2023).

Adverse events

While generally well-tolerated, adverse events associated with 5-MeO-DMT administration require careful consideration, particularly given the substance's potent and rapid effects, and can range from mild to potentially life-threatening (Wojtas, 2023).

The most critical safety concern involves potential toxic interactions and even death when 5-MeO-DMT is combined with harmala alkaloids, such as those found in ayahuasca, which are short-term monoamine oxidase inhibitors (Ragnhildstveit et al., 2023). Such interactions can lead to severe physical effects including epileptic seizures, pronounced muscle rigidity, and high fever (Ragnhildstveit et al., 2023). Research also suggests a potential for 5-MeO-DMT to induce epileptiform activity, particularly in regions like the temporal lobes, possibly linked to its 5-HT1A receptor agonist properties (Dourron et al., 2023). Beyond these physiological risks, the profound and rapid onset of 5-MeO-DMT's subjective effects can be overwhelming, leading to significant psychological challenges such as fear, extreme anxiety, and paranoia, which can make the experience difficult to navigate. Other reported adverse events include the late-onset of night terrors and physical manifestations like shivering or diarrhea (Ragnhildstveit et al., 2023).

In controlled clinical settings, mild and transient side effects are more commonly observed, often including acute nausea and headache, which typically resolve spontaneously (Millón et al., 2025). Subjective perceptual alterations, such as distortions in auditory and time perception, memory impairment, and feelings of perceptual isolation, are also reported. While disorienting, these are often short-lasting effects inherent to the psychedelic experience rather than purely negative adverse reactions (Ragnhildstveit et al., 2023; Reckweg et al., 2022). Despite the intensity of the experience and the range of potential adverse events, clinical studies and systematic reviews indicate that 5-MeO-DMT generally possesses a favorable short-term safety and tolerability profile. Clinical trials investigating inhaled 5-MeO-DMT for treatment-resistant depression reported moderate and spontaneously resolving adverse effects, with no life-threatening events (Wojtas, 2023). Similarly, a Phase I clinical trial using sublingual microdoses found the compound well-tolerated, with no significant adverse events or signs of organ toxicity (Millón et al., 2025). A systematic review of clinical trials further noted no serious adverse events or study drop-outs (Kwaśny et al., 2024).

How it differs from other psychadelics used in treatment of PTSD?

5-MeO-DMT differs significantly from other psychedelics used in PTSD treatment, such as ibogaine and classic serotonergic psychedelics like LSD or psilocybin, primarily in its pharmacological mechanism and phenomenological effects. Unlike most classic psychedelics, which primarily mediate therapeutic actions through 5-HT2A receptor activation, 5-MeO-DMT exhibits a markedly higher affinity for the 5-HT1A receptor (Ragnhildstveit et al., 2023). While it also modulates dopamine, glutamate, and GABA systems (Stavely, 2025), its primary mechanism of action does not involve the 5-HT2A receptor (Cherian et al., 2024). Phenomenologically, 5-MeO-DMT is characterized by a rapid onset, short duration, and intense mystical-type experiences often leading to ego dissolution with minimal visual effects (Davis et al., 2020; Ermakova et al., 2025).

Furthermore, recent research highlights that 5-MeO-DMT interacts with a more complex set of neurotransmitter receptors than classic psychedelics, contributing to its distinct therapeutic profile for conditions like PTSD (Stavely, 2025). A single administration of 5-MeO-DMT has been shown to produce rapid and sustained improvements in PTSD symptoms with next-day effects (Ragnhildstveit et al., 2023), and some therapeutic approaches even combine ibogaine and 5-MeO-DMT, suggesting a synergistic effect where ibogaine may prepare the nervous system for the intense "reset" facilitated by 5-MeO-DMT (Stavely, 2025).

Ibogaine

Ibogaine is an organic heteropentacyclic compound, specifically a monoterpenoid indole alkaloid and aromatic ether, functionally related to ibogamine. It is derived from the root bark of the Tabernanthe iboga or Voacanga africana plants, native to West-Central Africa. Ibogaine is classified as an oneirogen, a substance that creates dreams, and its chemical structure is a complex tricyclic indole molecule featuring an isoquinuclidine moiety (Cherian et al., 2024). The roots of the Tabernanthe iboga plant contain several psychotropic indole alkaloids, with its bark typically holding between 5% and 6% ibogaine (Underwood, 2025). This compound's lipophilic nature allows for its storage in fatty tissues, leading to a slow release (Cherian et al., 2024). Historically, the root bark of the iboga tree has been utilized for centuries in spiritual, medicinal, and rite of passage ceremonies within the Bwiti spiritual tradition of Gabon and Cameroon, and by the Fang people (Cherian et al., 2024; Yockey, 2025). In these ceremonial contexts, high doses of ibogaine are administered to induce hallucinations, facilitating psychological insight, emotional catharsis, and spiritual guidance (Ali et al., 2025; Yockey, 2025). Lower doses of iboga extracts have traditionally served as a stimulant to combat fatigue, hunger, and thirst during hunting expeditions (Ali et al., 2025). The first documented Western use of iboga occurred in the late 1800s by French explorers, eventually leading to its mid-20th-century application in France as an antidepressant and stimulant known as Lambarène before its subsequent prohibition (Cherian et al., 2024).

Mechanism of Action

Ibogaine's complex mechanism of action involves modulation of multiple neurotransmitter systems and a diverse array of receptors, including serotonin, dopamine, glutamate (Stavely, 2025), mu- and kappa-opioid, sigma-1 and sigma-2, and N-methyl-D-aspartate receptors. It also interacts with nicotinic acetylcholine receptors and inhibits voltage-gated ion channels (Ali et al., 2025).

A crucial aspect of ibogaine's neuropharmacology is its metabolism: it undergoes O-demethylation via cytochrome CYP2D6 enzymes in the gut wall and liver, producing its primary metabolite, noribogaine. While ibogaine has a plasma half-life of 4–7 hours, noribogaine's is considerably longer (28–49 hours) (Cherian et al., 2024). This prolonged presence is thought to significantly contribute to ibogaine's sustained therapeutic effects, acting as an effective antidepressant and alleviating cravings (Underwood, 2025). Like ibogaine, noribogaine also exhibits moderate-to-weak affinity for various neurotransmitter receptors, including mu- and kappa-opioid, dopamine and serotonin transporters, NMDA, nicotinic acetylcholine, and sigma-1 and sigma-2 receptors (Ali et al., 2025).

Specifically, the NMDA receptor antagonism by both ibogaine and noribogaine is hypothesized to facilitate the "unlearning" of fixed perceptions and responses, which is particularly relevant in addressing cravings and environmental cues associated with substance use disorders (Cherian et al., 2024; Underwood, 2025). Furthermore, ibogaine's agonism at kappa-opioid receptors may contribute to its efficacy in treating substance use disorder and withdrawal symptoms (Cherian et al., 2024). Unlike classical psychedelics such as LSD or psilocybin, ibogaine's mechanism of action does not primarily involve the 5-HT2A receptor (Cherian et al., 2024).

Beyond receptor interactions, ibogaine also influences neuroplasticity by promoting the expression of neurotrophic factors such as glial cell-derived neurotrophic factor in the ventral tegmental area and brain-derived neurotrophic factor in the prefrontal cortex. These neuroplastic effects, along with its ability to stabilize the inward-open conformation of the serotonin transporter, may underpin its proposed therapeutic actions (Ali et al., 2025). Ibogaine has also been shown to possess anti-inflammatory and antioxidant properties (Cherian et al., 2024).

Efficiency

While its precise mechanism of action remains incompletely elucidated, ibogaine's anti-addictive properties are likely mediated by its polypharmacological profile, influencing numerous CNS receptors, including N-methyl-D-aspartate, kappa and mu-opioid, and sigma-2 receptor sites (Cherian et al., 2024; Vorobyeva & Kozlova, 2022). Beyond addiction, ibogaine also shows promise in the treatment of Post-Traumatic Stress Disorder and co-occurring conditions such as depression and anxiety (Cherian et al., 2024). Observational studies, particularly involving Special Operations Forces Veterans with combat-related PTSD, show promising results. A retrospective survey of 65 SFVs who received combined ibogaine and 5-MeO-DMT therapy demonstrated significant reductions in PTSD symptoms, depression, cognitive impairment, and suicidal ideation, a critical finding given the higher rates of suicidality in veteran populations (Cherian et al., 2024; Davis et al., 2020). This treatment sometimes led to reported PTSD remission rates of up to 86% one month post-treatment. Another observational study involving 86 SFVs similarly reported significant reductions in self-reported PTSD and depression symptoms. While these preliminary findings are encouraging, especially for traditionally treatment-resistant individuals, it is crucial to recognize that the current evidence primarily stems from observational studies. Therefore, further double-blind, placebo-controlled randomized controlled trials with larger sample sizes are necessary to fully establish ibogaine's safety and efficacy for PTSD (Cherian et al., 2024).

Quality of Life and Patient Satisfaction

Beyond symptom reduction, ibogaine treatment is associated with substantial improvements in patients' overall quality of life and satisfaction with their mental health outcomes, with recent studies reporting significant positive changes in personal well-being, life's purpose and meaning, social relationships, attitudes about life and self, mood, behavior, and spirituality (Davis et al., 2020; Yockey, 2025). A qualitative study involving 73 individuals also documented long-lasting psychological benefits, including enhanced emotional regulation, increased meaning in life, and greater authenticity, indicating ibogaine's potential to improve psychological well-being beyond mere cessation of substance use (Yockey, 2025). Furthermore, a recent observational study showed that ibogaine, when co-administered with magnesium, significantly reduced overall disability as measured by the World Health Organization Disability Assessment Schedule 2.0. Immediately after treatment, participants improved from mild-to-moderate disability to borderline no-to-mild disability, with most achieving no disability one month post-treatment (Cherian et al., 2024).

Adverse events

Despite its therapeutic potential, ibogaine presents significant safety concerns, necessitating careful patient selection and monitoring during its administration. Its most critical safety issue is cardiotoxicity, where ibogaine prolongs the QT interval on electrocardiograms by inhibiting hERG potassium channels (Ali et al., 2025; Cherian et al., 2024; Yockey, 2025). This increases the risk of fatal arrhythmias, such as torsades de pointes, particularly in individuals with underlying cardiovascular disease, pre-existing prolonged QT interval, hERG mutations, electrolyte imbalances, or concurrent substance use (Cherian et al., 2024; Underwood, 2025; Yockey, 2025). Cardiac abnormalities, including ventricular tachyarrhythmias and prolonged QT intervals, have also been observed in patients without a history of cardiovascular conditions. Coadministration of magnesium with ibogaine may help reduce this cardiotoxicity risk (Cherian et al., 2024).

Beyond cardiovascular risks, ibogaine exhibits neurotoxicity at high doses in preclinical models, potentially causing damage to cerebellar Purkinje cells (Ali et al., 2025; Underwood, 2025; Yockey, 2025). In humans, adverse neurological events reported include ataxia, tremors, and psychosis, with rare instances of mania or psychosis noted primarily in unregulated treatment settings (Cherian et al., 2024; Yockey, 2025). While physical symptoms like ataxia and vomiting can occur, participants often do not report being particularly alarmed or bothered by them, possibly due to ibogaine's ability to maintain a lucid sense of place and time during the experience (Stavely, 2025). The drug's complex pharmacokinetics, characterized by a long half-life

and active metabolites, further complicate dosing and contribute to toxicity risks, especially with inadequate medical supervision, polypharmacy, or pre-existing health conditions (Yockey, 2025). These inherent safety risks underscore the critical importance of comprehensive medical screening, careful patient selection, and robust risk mitigation strategies for any ibogaine treatment (Stavely, 2025). Consequently, ibogaine is classified as a Schedule I substance in the United States, limiting research and clinical use due to its high potential for abuse and lack of accepted medical utility (Yockey, 2025).

How it differs from other psychadelics used in treatment of PTSD?

Ibogaine's distinctive mechanism of action, involving a complex interaction with multiple neurotransmitter systems and its long-acting metabolite noribogaine, sets it apart from more commonly studied psychedelics like MDMA or psilocybin. Unlike MDMA, which primarily functions by promoting the release of serotonin, dopamine, and norepinephrine, and acting as a weak 5-HT1 and 5-HT2 receptor agonist to enhance empathy and facilitate trauma processing in psychotherapy (Bird et al., 2021; Tedesco et al., 2021; Varker et al., 2021), ibogaine's effects stem from its high affinity for k-opioid, m-opioid, N-methyl-D-aspartate, and sigma-2 receptors, alongside inhibiting voltage-gated ion channels (Cherian et al., 2024; Davis et al., 2020; Vorobyeva & Kozlova, 2022). Its NMDA antagonism and k-opioid agonism are particularly crucial for its efficacy in substance use disorder and withdrawal, further influencing neurotrophic factors that contribute to its anti-addictive and antidepressant properties (Cherian et al., 2024). Similarly, psilocybin, after being metabolized to psilocin, acts predominantly as an agonist at serotonin 5-HT2A receptors, leading to altered perception, emotional modulation, and neuroplasticity (Choi et al., 2024; Varker et al., 2021). Furthermore, ibogaine's experience is characterized by intensified memory recollections, particularly related to substance use, and a sense of "brain resetting," often with pronounced physical effects such as ataxia and vomiting (Underwood, 2025). However, unlike heroic doses of other classic psychedelics that can lead to disorientation, ibogaine often allows participants to maintain a lucid sense of place and time, potentially mitigating the risk of a "bad trip" (Stavely, 2025). This multifaceted neuropharmacological profile, which is not a conventional dopamine or opioid agonist/antagonist or a monoamine reuptake inhibitor, differentiates ibogaine significantly from the serotonin-centric mechanisms of MDMA and psilocybin (Underwood, 2025).

Discussion

The aim of this systematic review was to assess the efficacy of psilocybin, MDMA, ketamine, ibogaine, and 5-MeO-DMT for the treatment of PTSD in adults. Among these psychedelics, MDMA-assisted psychotherapy has demonstrated robust efficacy, with Phase 3 studies showing significant reductions in PTSD symptom severity, increased response and remission rates, and improvements in functional impairment (Sippel et al., 2024). The FDA has granted MDMA a "breakthrough therapy" designation due to its durable benefits (Krediet et al., 2020; Sippel et al., 2024). Results from the first Phase 3 multi-site study confirmed the safety and efficacy of MDMA-assisted therapy in individuals with severe PTSD, with 67%–71% of participants losing the PTSD diagnosis after treatment, compared to 32%–48% with placebo-assisted therapy (Van Der Kolk et al., 2024; Wolfgang et al., 2025). Long-term follow-up studies, some extending to an average of 42 months post-treatment, indicate stable positive outcomes in areas such as improved relationships, enhanced spiritual life, enriched community involvement, augmented empathy for others, and increased creativity, all contributing to post-traumatic growth (Feduccia et al., 2018; Krediet et al., 2020). A pooled analysis of 105 patients from six randomized controlled trials further showed that MDMA-treated patients had significantly greater reductions in PTSD symptom scores and demonstrated higher effect sizes with significantly lower dropout rates compared to data used for the FDA approval of paroxetine and sertraline (Krediet et al., 2020).

Ketamine also exhibits promising short-term efficacy, with studies showing substantial reductions in PTSD symptoms, particularly at higher doses, and its potential as an effective adjunct to psychotherapy (Almeida et al., 2024; Beaglehole et al., 2025). For instance, a double-blind active-controlled randomized crossover study provided preliminary support for the efficacy and tolerability of intramuscular ketamine in treatment-resistant PTSD, noting that further research is required to establish optimal dosing and long-term effects (Beaglehole et al., 2025). However, the quality of evidence for ketamine combined with psychotherapy is currently graded as "low" based on small randomized controlled trials with methodological limitations, while evidence for ketamine as a stand-alone treatment is considered "very low" (Varker et al., 2021).

For psilocybin, a Phase 2 nonrandomized, open-label, multicenter trial reported rapid and sustained reductions in PTSD symptoms, improved functioning, and enhanced quality of life over a 12-week period (Choi et al., 2024; McGowan et al., 2025). This study highlighted the need for larger, controlled studies to

fully understand the safety and efficacy of psilocybin for PTSD, noting limitations such as the exclusion of participants with complex PTSD or high suicide risk (McGowan et al., 2025). Clinical trials specifically focusing on PTSD treatment with psilocybin are generally still lacking, and its effects can be more variable and less predictable compared to MDMA (Krediet et al., 2020).

Ibogaine offers unique benefits, including long-lasting psychological improvements such as enhanced emotional regulation, increased meaning in life, and greater authenticity (Yockey, 2025). A recent observational study also demonstrated a notable reduction in overall disability post-treatment when ibogaine was co-administered with magnesium, improving participants from mild-to-moderate disability to borderline no-to-mild disability immediately after treatment, with most achieving no disability one month later (Cherian et al., 2024). Participants in a study reported significant and large reductions in PTSD, depression, and anxiety symptoms, suicidal ideation, and cognitive impairment following ibogaine treatments (Davis et al., 2020). While observational studies suggest promise for ibogaine, robust double-blind, placebo-controlled randomized controlled trials with large sample sizes have yet to be conducted, and research on ibogaine is still in its infancy compared to other psychedelics (Cherian et al., 2024; Yockey, 2025). NMDA antagonism and k-opioid agonism are particularly crucial for its efficacy (Cherian et al., 2024).

Similarly, 5-MeO-DMT shows therapeutic potential, with observational studies indicating improvements in PTSD symptoms and increased life satisfaction (Davis et al., 2020; Ragnhildstveit et al., 2023). A case study highlighted its fast-acting and sustained symptom reduction in chronic refractory cases, accompanied by marked reductions in hopelessness and related suicide risk, with improvements sustained at 1-, 3-, 6-, and 12-month follow-ups (Ragnhildstveit et al., 2023). However, case studies are inherently limited and not generalizable to broader populations, with further research warranted to replicate and extend these preliminary findings using clinically accepted methods (Ragnhildstveit et al., 2023). Participants in a study reported significant and large reductions in PTSD, depression, and anxiety symptoms, suicidal ideation, and cognitive impairment following ibogaine and 5-MeO-DMT treatments (Davis et al., 2020).

While the exact mechanisms and long-term data vary across these psychedelics, all demonstrate promising efficacy in ameliorating PTSD symptoms and enhancing aspects of patient well-being, though further research is warranted to establish optimal protocols and comprehensive safety profiles for each substance.

Conclusions

The latest research signals a paradigm shift in PTSD treatment, moving beyond symptom management towards psychedelic-assisted therapies that offer the potential for sustained remission. Among these, MDMA-assisted psychotherapy stands out due to its robust efficacy, evidenced by successful Phase 3 trials demonstrating significant reductions in PTSD symptom severity, increased response and remission rates, and improvements in functional impairment (Sippel et al., 2024). Notably, 67%–71% of participants in these trials lost their PTSD diagnosis after treatment, a marked improvement over the 32%–48% seen with placebo-assisted therapy (Van Der Kolk et al., 2024; Wolfgang et al., 2025). This efficacy, coupled with durable benefits, earned MDMA an FDA "breakthrough therapy" designation (Sippel et al., 2024). Long-term follow-up studies, extending up to 42 months post-treatment, further indicate stable positive outcomes, including improved relationships, enhanced spiritual life, and increased creativity, contributing to post-traumatic growth (Feduccia et al., 2018; Krediet et al., 2020). A pooled analysis of 105 patients from six randomized controlled trials reinforces these findings, showing MDMA-treated patients experienced significantly greater reductions in PTSD symptom scores and higher effect sizes with lower dropout rates compared to conventional treatments like paroxetine and sertraline (Krediet et al., 2020).

While MDMA leads in evidence, other psychedelics also show promise. Ketamine exhibits promising short-term efficacy, particularly at higher doses, with preliminary support for its use in treatment-resistant PTSD, though more research is needed to establish optimal dosing and long-term effects (Almeida et al., 2024; Beaglehole et al., 2025). Psilocybin has shown rapid and sustained reductions in PTSD symptoms, improved functioning, and enhanced quality of life in a Phase 2 trial, highlighting the need for larger, controlled studies (McGowan et al., 2025). Ibogaine offers unique benefits, including long-lasting psychological improvements and significant reductions in PTSD, depression, and anxiety symptoms, although robust double-blind, placebo-controlled trials are still in their early stages (Cherian et al., 2024; Davis et al., 2020; Yockey, 2025). Similarly, 5-MeO-DMT has demonstrated improvements in PTSD symptoms and increased life satisfaction in observational studies and case reports, but these findings require further validation through clinically accepted methods (Davis et al., 2020; Ragnhildstveit et al., 2023).

The insights presented in this paper underscore a pivotal moment in the evolution of PTSD treatment, highlighting the profound potential of psychedelic-assisted therapies to offer sustained remission rather than mere symptom management. However, realizing this potential hinges upon rigorous and expanded research efforts. A significant challenge in this nascent field is the limited quantity of high-quality evidence, with many promising findings still derived from observational studies, case reports, or smaller trials, rather than robust double-blind, placebo-controlled randomized clinical trials (Cherian et al., 2024; Ragnhildstveit et al., 2023; Yockey, 2025). Furthermore, widespread legal restrictions and the classification of many psychedelics as Schedule I substances in numerous countries severely impede research, hindering access for scientific inquiry and therapeutic development. For instance, the US Controlled Substances Act of 1970 and similar legislation in other nations have historically restricted the use of psychedelics in research, with their Schedule I status still hampering researchers' ability to effectively study their risks and benefits and precluding federal funding (Bird et al., 2021; Davis et al., 2020; Miller & Zoladz, 2024; Wolfgang et al., 2025). Future endeavors must therefore not only delve deeper into the neurobiological and psychological mechanisms through which these drugs exert their effects, identify optimal therapeutic protocols, and establish comprehensive safety profiles for each substance, but also advocate for policy changes to address these regulatory barriers.

Exploring personalized treatment plans is also key, as individual responses to psychedelics and the varied presentations of PTSD necessitate tailored approaches to achieve the best possible outcomes.

Urgent large-scale, well-designed clinical trials are needed to confirm the efficacy and safety of these treatments across diverse populations, ultimately aiming to ensure equitable access to these innovative options.

REFERENCES

1. Abdallah, C. G., Roache, J. D., Gueorguieva, R., Averill, L. A., Young-McCaughan, S., Shiroma, P., Purohit, P., Brundige, A., Murff, W., Ahn, K.-H., Sherif, M., Baltutis, E. J., Ranganathan, M., D'Souza, D. C., Martini, B., Southwick, S. M., Petrakis, I. L., Burson, R. R., Guthmiller, K. B., … Krystal, J. H. (2022). Dose-related effects of ketamine for antidepressant-resistant symptoms of posttraumatic stress disorder in veterans and active duty military: a double-blind, randomized, placebo-controlled multi-center clinical trial. *Neuropsychopharmacology*, *47*(8), 1574. https://doi.org/10.1038/s41386-022-01266-9
2. Ali, S., Tian, X., Cunningham, K. A., & Zhou, J. (2025). Old Dog, New Tricks: Ibogaine and Its Analogs as Potential Neurotherapeutics. *Journal of Medicinal Chemistry*, *68*(18), 18744. https://doi.org/10.1021/acs.jmedchem.5c02510
3. Almeida, T. M., Martins, M., Cordeiro, Q., & Uchida, R. R. (2024). *EFFECTIVENESS OF KETAMINE FOR THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER – A SYSTEMATIC REVIEW AND META-ANALYSIS*. https://doi.org/10.36131/cnfioritieditore20240102
4. Andualem, F., Melkam, M., Takelle, G. M., Nakie, G., Tinsae, T., Fentahun, S., Rtbey, G., Begashaw, T. D., Seid, J., Tegegn, L. F., Gedef, G. M., Bitew, D. A., & Godana, T. N. (2024). Prevalence of posttraumatic stress disorder and associated factors among displaced people in Africa: a systematic review and meta-analysis [Review of *Prevalence of posttraumatic stress disorder and associated factors among displaced people in Africa: a systematic review and meta-analysis*]. *Frontiers in Psychiatry*, *15*, 1336665. Frontiers Media. https://doi.org/10.3389/fpsyt.2024.1336665
5. Askariyan, K., Joghataei, M. T., Dehghan, S., Nohesara, S., Rihipour, L., Mohammadi, M. H., & Ahmadirad, N. (2025). An overview of psilocybin, LSD, MDMA, and ketamine in revitalizing psychedelic-assisted therapy: Insights, limitations and future directions [Review of *An overview of psilocybin, LSD, MDMA, and ketamine in revitalizing psychedelic-assisted therapy: Insights, limitations and future directions*]. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 111461. Elsevier BV. https://doi.org/10.1016/j.pnpbp.2025.111461
6. Azevedo, M., Martinho, R., Oliveira, A., Correia-de-Sá, P., & Moreira-Rodrigues, M. (2024). Molecular pathways underlying sympathetic autonomic overshooting leading to fear and traumatic memories: looking for alternative therapeutic options for post-traumatic stress disorder [Review of *Molecular pathways underlying sympathetic autonomic overshooting leading to fear and traumatic memories: looking for alternative therapeutic options for post-traumatic stress disorder*]. *Frontiers in Molecular Neuroscience*, *16*. Frontiers Media. https://doi.org/10.3389/fnmol.2023.1332348
7. Beaglehole, B., Glue, P., Neehoff, S., Shadli, S., McNaughton, N., Kimber, B., Muirhead, C., De Bie, A., Day-Brown, R., & Hughes-Medlicott, N. J. (2025). Ketamine for treatment-resistant post-traumatic stress disorder: double-blind active-controlled randomised crossover study. *BJPsych Open*, *11*(6). https://doi.org/10.1192/bjo.2025.10854
8. Bell, R. F., & Kalso, E. (2018). Ketamine for pain management. *PAIN Reports*, *3*(5). https://doi.org/10.1097/pr9.0000000000000674

9. Benzenhöfer, U., & Passie, T. (2010). Rediscovering MDMA (ecstasy): the role of the American chemist Alexander T. Shulgin. *Addiction*, *105*(8), 1355. https://doi.org/10.1111/j.1360-0443.2010.02948.x
10. Bird, C. I. V., Modlin, N. L., & Rucker, J. J. H. (2021). Psilocybin and MDMA for the treatment of trauma-related psychopathology. *International Review of Psychiatry*, *33*(3), 229. https://doi.org/10.1080/09540261.2021.1919062
11. Bryant, R. A., Nickerson, A., Morina, N., & Liddell, B. J. (2023). Posttraumatic Stress Disorder in Refugees [Review of *Posttraumatic Stress Disorder in Refugees*]. *Annual Review of Clinical Psychology*, *19*(1), 413. Annual Reviews. https://doi.org/10.1146/annurev-clinpsy-080921-080359
12. Carlson, E. B., Shieh, L., Barlow, M., Palmieri, P. A., Yen, F., Mellman, T. A., Williams, M., Williams, M. Y., Chandran, M., & Spain, D. A. (2023). Mental health symptoms are comparable in patients hospitalized with acute illness and patients hospitalized with injury. *PLoS ONE*, *18*(9). https://doi.org/10.1371/journal.pone.0286563
13. Charney, D. S. (1993). Psychobiologic Mechanisms of Posttraumatic Stress Disorder [Review of *Psychobiologic Mechanisms of Posttraumatic Stress Disorder*]. *Archives of General Psychiatry*, *50*(4), 294. American Medical Association. https://doi.org/10.1001/archpsyc.1993.01820160064008
14. Cherian, K., Shinozuka, K., Tabaac, B. J., Arenas, A., Beutler, B. D., Evans, V. D., Fasano, C., & Muir, O. S. (2024). Psychedelic Therapy: A Primer for Primary Care Clinicians—Ibogaine. *American Journal of Therapeutics*, *31*(2). https://doi.org/10.1097/MJT.0000000000001723
15. Chiu, H. T. S., Chan, A. H. T., & Meiser-Stedman, R. (2023). Relationship Between Anxiety Sensitivity and Post-Traumatic Stress Symptoms in Trauma-Exposed Children and Adolescents: A Meta-Analysis. *Cognitive Therapy and Research*, *48*(3), 371. https://doi.org/10.1007/s10608-023-10427-z
16. Choi, C. Q., Johnson, D. E., Chen-Li, D., & Rosenblat, J. D. (2024). Mechanisms of psilocybin on the treatment of posttraumatic stress disorder [Review of *Mechanisms of psilocybin on the treatment of posttraumatic stress disorder*]. *Journal of Psychopharmacology*. SAGE Publishing. https://doi.org/10.1177/02698811241286771
17. Colcott, J., Guerin, A. A., Carter, O., Meikle, S., & Bedi, G. (2024). Side-effects of mdma-assisted psychotherapy: a systematic review and meta-analysis. *Neuropsychopharmacology*, *49*(8), 1208. https://doi.org/10.1038/s41386-024-01865-8
18. Court, R. C. V., Wiseman, M. S., Meyer, K., Ballhorn, D. J., Amses, K. R., Slot, J. C., Dentinger, B. T. M., Garibay-Orijel, R., & Uehling, J. K. (2022). Diversity, biology, and history of psilocybin-containing fungi: Suggestions for research and technological development [Review of *Diversity, biology, and history of psilocybin-containing fungi: Suggestions for research and technological development*]. *Fungal Biology*, *126*(4), 308. Elsevier BV. https://doi.org/10.1016/j.funbio.2022.01.003
19. Daniel, J., & Haberman, M. (2017). Clinical potential of psilocybin as a treatment for mental health conditions. *Mental Health Clinician*, *7*(1), 24. https://doi.org/10.9740/mhc.2017.01.024
20. Davis, A. K., Averill, L. A., Sepeda, N. D., Barsuglia, J. P., & Amoroso, T. (2020). Psychedelic Treatment for Trauma-Related Psychological and Cognitive Impairment Among US Special Operations Forces Veterans. *Chronic Stress*, *4*. https://doi.org/10.1177/2470547020939564
21. Davis, L. L., Schein, J., Cloutier, M., Gagnon-Sanschagrin, P., Maitland, J., Urganus, A., Guérin, A., Lefèbvre, P., & Houle, C. R. (2022). The Economic Burden of Posttraumatic Stress Disorder in the United States From a Societal Perspective. *The Journal of Clinical Psychiatry*, *83*(3). https://doi.org/10.4088/jcp.21m14116
22. Day, J., & Agrawal, D. K. (2025). *High and Low Dose Ketamine in Post-Traumatic Stress Disorder*. https://doi.org/10.26502/acc.078
23. Dodd, S., Norman, T. R., Eyre, H. A., Stahl, S. M., Phillips, A., Carvalho, A. F., & Berk, M. (2022). Psilocybin in neuropsychiatry: a review of its pharmacology, safety, and efficacy [Review of *Psilocybin in neuropsychiatry: a review of its pharmacology, safety, and efficacy*]. *CNS Spectrums*, *28*(4), 416. Cambridge University Press. https://doi.org/10.1017/s1092852922000888
24. Dourron, H. M., Nichols, C. D., Simonsson, O., Bradley, M., Carhart-Harris, R., & Hendricks, P. S. (2023). 5-MeO-DMT: An atypical psychedelic with unique pharmacology, phenomenology & risk? [Review of *5-MeO-DMT: An atypical psychedelic with unique pharmacology, phenomenology & risk?*]. *Psychopharmacology*, *242*(7), 1457. Springer Science+Business Media. https://doi.org/10.1007/s00213-023-06517-1
25. Du, J., Diao, H., Zhou, X., Zhang, C., Chen, Y., Gao, Y., & Wang, Y. (2022). Post-traumatic stress disorder: a psychiatric disorder requiring urgent attention [Review of *Post-traumatic stress disorder: a psychiatric disorder requiring urgent attention*]. *Medical Review*, *2*(3), 219. De Gruyter. https://doi.org/10.1515/mr-2022-0012
26. Ermakova, A. O., Dunbar, F., Rucker, J., & Johnson, M. W. (2021). A narrative synthesis of research with 5-MeO-DMT [Review of *A narrative synthesis of research with 5-MeO-DMT*]. *Journal of Psychopharmacology*, *36*(3), 273. SAGE Publishing. https://doi.org/10.1177/02698811211050543
27. Ermakova, A. O., Dunbar, F., Seynaeve, M., & Millière, R. (2025). Mapping the phenomenology of intranasal 5-MeO-DMT in psychedelic-naïve healthy adults. *Scientific Reports*, *15*(1), 38874. https://doi.org/10.1038/s41598-025-22620-z
28. Feduccia, A. A., Holland, J., & Mithoefer, M. C. (2017). Progress and promise for the MDMA drug development program. *Psychopharmacology*, *235*(2), 561. https://doi.org/10.1007/s00213-017-4779-2

29. Ferretti, F., Pozza, A., Bossini, L., Desantis, S., Olivola, M., Matto, L. D., Gualtieri, G., Gusinu, R., Bezzini, D., Fagiolini, A., & Coluccia, A. (2019). Post-traumatic stress disorder in Italy: a comprehensive evaluation of all the ICD comorbidities and gender-related differences. *BMC Research Notes*, *12*(1). https://doi.org/10.1186/s13104-019-4792-0
30. First, M. B., Clarke, D. E., Yousif, L. H., Eng, A. M., Gogtay, N., & Appelbaum, P. S. (2022). DSM-5-TR: Rationale, Process, and Overview of Changes. *Psychiatric Services*, *74*(8), 869. https://doi.org/10.1176/appi.ps.20220334
31. Freudenmann, R. W., Öxler, F., & Bernschneider-Reif, S. (2006). The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents*. *Addiction*, *101*(9), 1241. https://doi.org/10.1111/j.1360-0443.2006.01511.x
32. Fuller, R. G., Kikla, E. M., Fawcett, A. P. W., Hesling, J. D., Keenan, S., Flarity, K., Patzkowski, M. S., April, M. D., Bebarta, V. S., & Schauer, S. G. (2024). Low-dose ketamine for acute pain: A narrative review [Review of *Low-dose ketamine for acute pain: A narrative review*]. *The American Journal of Emergency Medicine*, *86*, 41. Elsevier BV. https://doi.org/10.1016/j.ajem.2024.09.033
33. Fung, H. W., Leousi, A., Chau, A. K. C., Sit, K. Y., Lam, C. C., Li, C. M., Huang, C. H. O., Cheung, C. T. Y., Lam, S. K. K., Wang, E. K. S., & Ho, G. W. K. (2025). Prevalence of ICD-11 post-traumatic stress disorder (PTSD) and complex PTSD in the general populations: A systematic review and meta-analysis [Review of *Prevalence of ICD-11 post-traumatic stress disorder (PTSD) and complex PTSD in the general populations: A systematic review and meta-analysis*]. *Asian Journal of Psychiatry*, *110*, 104610. Elsevier BV. https://doi.org/10.1016/j.ajp.2025.104610
34. Gibuła-Tarłowska, E., Wiszniewska, A., Turyk, M., Szymczyk, P., Kotlińska, J. H., & Kędzierska, E. (2025). Ketamine—From an Anesthetic to a Psychiatric Drug: Mechanisms of Action, Clinical Applications and Potential Risks [Review of *Ketamine—From an Anesthetic to a Psychiatric Drug: Mechanisms of Action, Clinical Applications and Potential Risks*]. *Molecules*, *30*(13), 2824. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/molecules30132824
35. Glatfelter, G. C., Pottie, E., Partilla, J. S., Sherwood, A. M., Kaylo, K. W., Pham, D. N. K., Naeem, M., Sammeta, V. R., DeBoer, S., Golen, J. A., Hulley, E. B., Stove, C. P., Chadeayne, A. R., Manke, D. R., & Baumann, M. H. (2022). Structure–Activity Relationships for Psilocybin, Baeocystin, Aeruginascin, and Related Analogues to Produce Pharmacological Effects in Mice. *ACS Pharmacology & Translational Science*, *5*(11), 1181. https://doi.org/10.1021/acsptsci.2c00177
36. Golitaleb, M., Mazaheri, E., Bonyadi, M., & Sahebi, A. (2022). Prevalence of Post-traumatic Stress Disorder After Flood: A Systematic Review and Meta-Analysis [Review of *Prevalence of Post-traumatic Stress Disorder After Flood: A Systematic Review and Meta-Analysis*]. *Frontiers in Psychiatry*, *13*, 890671. Frontiers Media. https://doi.org/10.3389/fpsyt.2022.890671
37. Greer, G., & Tolbert, R. (1986). Subjective Reports of the Effects of MDMA in a Clinical Setting. *Journal of Psychoactive Drugs*, *18*(4), 319. https://doi.org/10.1080/02791072.1986.10472364
38. Greer, G., & Tolbert, R. (1990). The Therapeutic Use of MDMA. In *Topics in the neurosciences* (p. 21). Springer Nature. https://doi.org/10.1007/978-1-4613-1485-1_2
39. Greer, G., & Tolbert, R. (1998). A Method of Conducting Therapeutic Sessions with MDMA. *Journal of Psychoactive Drugs*, *30*(4), 371. https://doi.org/10.1080/02791072.1998.10399713
40. Handiso, D. W., Belsti, Y., Boyle, J., Paul, E., Shawyer, F., & Enticott, J. (2023). A Systematic Review and Meta-Analysis of Longitudinal Studies on Posttraumatic Stress Disorders in Refugees and Asylum Seekers [Review of *A Systematic Review and Meta-Analysis of Longitudinal Studies on Posttraumatic Stress Disorders in Refugees and Asylum Seekers*]. *International Journal of Mental Health and Addiction*. Springer Science+Business Media. https://doi.org/10.1007/s11469-023-01172-1
41. Harnett, N. G., Goodman, A. M., & Knight, D. C. (2020). PTSD-related neuroimaging abnormalities in brain function, structure, and biochemistry [Review of *PTSD-related neuroimaging abnormalities in brain function, structure, and biochemistry*]. *Experimental Neurology*, *330*, 113331. Elsevier BV. https://doi.org/10.1016/j.expneurol.2020.113331
42. Hayes, J. P., VanElzakker, M. B., & Shin, L. M. (2012). Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies [Review of *Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies*]. *Frontiers in Integrative Neuroscience*, *6*, 89. Frontiers Media. https://doi.org/10.3389/fnint.2012.00089
43. Hinojosa, C. A., George, G., & Ben-Zion, Z. (2024). Neuroimaging of posttraumatic stress disorder in adults and youth: progress over the last decade on three leading questions of the field [Review of *Neuroimaging of posttraumatic stress disorder in adults and youth: progress over the last decade on three leading questions of the field*]. *Molecular Psychiatry*, *29*(10), 3223. Springer Nature. https://doi.org/10.1038/s41380-024-02558-w
44. Hirota, K., & Lambert, D. G. (2022). Ketamine; history and role in anesthetic pharmacology [Review of *Ketamine; history and role in anesthetic pharmacology*]. *Neuropharmacology*, *216*, 109171. Elsevier BV. https://doi.org/10.1016/j.neuropharm.2022.109171
45. Hofmann, A., Frey, A., Ott, H., Petrzilka, Th., & Troxler, F. (1958). Konstitutionsaufklärung und Synthese von Psilocybin. *Cellular and Molecular Life Sciences*, *14*(11), 397. https://doi.org/10.1007/bf02160424

46. Holas, P., & Kamińska, J. (2023). Mindfulness meditation and psychedelics: potential synergies and commonalities [Review of *Mindfulness meditation and psychedelics: potential synergies and commonalities*]. *Pharmacological Reports*, *75*(6), 1398. Elsevier BV. https://doi.org/10.1007/s43440-023-00551-8
47. Iqbal, J., Huang, G.-D., Xue, Y.-X., Yang, M., & Jia, X. (2023). The neural circuits and molecular mechanisms underlying fear dysregulation in posttraumatic stress disorder. *Frontiers in Neuroscience*, *17*, 1281401. https://doi.org/10.3389/fnins.2023.1281401
48. Irizarry, R., Winczura, A., Dimassi, O., Dhillon, N., Minhas, A., & Larice, J. (2022). Psilocybin as a Treatment for Psychiatric Illness: A Meta-Analysis. *Cureus*. https://doi.org/10.7759/cureus.31796
49. IsHak, W. W., García, P., Pearl, R., Dang, J., William, C., Totlani, J., & Danovitch, I. (2023). The Impact of Psilocybin on Patients Experiencing Psychiatric Symptoms: A Systematic Review of Randomized Clinical Trials. [Review of *The Impact of Psilocybin on Patients Experiencing Psychiatric Symptoms: A Systematic Review of Randomized Clinical Trials.*]. *PubMed*, *20*, 39. National Institutes of Health. https://pubmed.ncbi.nlm.nih.gov/37387703
50. Jefferson, S. J., Gregg, I., Dibbs, M., Liao, C., Wu, H., Davoudian, P. A., Woodburn, S. C., Wehrle, P. H., Sprouse, J., Sherwood, A. M., Kaye, A. P., Pittenger, C., & Kwan, A. C. (2023). 5-MeO-DMT modifies innate behaviors and promotes structural neural plasticity in mice. *Neuropsychopharmacology*, *48*(9), 1257. https://doi.org/10.1038/s41386-023-01572-w
51. Johnston, J. N., Kadriu, B., Kraus, C., Henter, I. D., & Zarate, C. A. (2023). Ketamine in neuropsychiatric disorders: an update [Review of *Ketamine in neuropsychiatric disorders: an update*]. *Neuropsychopharmacology*, *49*(1), 23. Springer Nature. https://doi.org/10.1038/s41386-023-01632-1
52. Jones, K., Boschen, M. J., Devilly, G. J., Vogler, J., Flowers, H., Winkleman, C., & Wullschleger, M. (2024). Risk and protective factors that predict posttraumatic stress disorder after traumatic injury: A systematic review [Review of *Risk and protective factors that predict posttraumatic stress disorder after traumatic injury: A systematic review*]. *Health Sciences Review*, *10*, 100147. Elsevier BV. https://doi.org/10.1016/j.hsr.2023.100147
53. Jowf, G. I. A., Ahmed, Z. T., An, N., Reijnders, R. A., Ambrosino, E., Rutten, B. P. F., Nijs, L. de, & Eijssen, L. (2022). A Public Health Perspective of Post-Traumatic Stress Disorder [Review of *A Public Health Perspective of Post-Traumatic Stress Disorder*]. *International Journal of Environmental Research and Public Health*, *19*(11), 6474. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/ijerph19116474
54. Kaminski, D., & Reinert, J. P. (2023). The Tolerability and Safety of Psilocybin in Psychiatric and Substance-Dependence Conditions: A Systematic Review [Review of *The Tolerability and Safety of Psilocybin in Psychiatric and Substance-Dependence Conditions: A Systematic Review*]. *Annals of Pharmacotherapy*, *58*(8), 811. SAGE Publishing. https://doi.org/10.1177/10600280231205645
55. Kargbo, R. B., Sherwood, A. M., Walker, A. J., Cozzi, N. V., Dagger, R. E., Sable, J., O'Hern, K., Kaylo, K. W., Patterson, T., Tarpley, G., & Meisenheimer, P. (2020). Direct Phosphorylation of Psilocin Enables Optimized cGMP Kilogram-Scale Manufacture of Psilocybin. *ACS Omega*, *5*(27), 16959. https://doi.org/10.1021/acsomega.0c02387
56. Khsim, I. E. F., Rodríguez, M. M., Riquelme-Gallego, B., Caparrós-González, R. A., & Amezcua-Prieto, C. (2022). Risk Factors for Post-Traumatic Stress Disorder after Childbirth: A Systematic Review [Review of *Risk Factors for Post-Traumatic Stress Disorder after Childbirth: A Systematic Review*]. *Diagnostics*, *12*(11), 2598. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/diagnostics12112598
57. Koenen, K. C., Ratanatharathorn, A., Ng, L. C., McLaughlin, K. A., Bromet, E. J., Stein, D. J., Karam, E. G., Ruscio, A. M., Benjet, C., Scott, K. M., Atwoli, L., Petukhova, M., Lim, C., Aguilar-Gaxiola, S., Malik, A., Alonso, J., Bunting, B., Ciutan, M., Girolamo, G. de, … Kessler, R. C. (2017). Posttraumatic stress disorder in the World Mental Health Surveys. *Psychological Medicine*, *47*(13), 2260. https://doi.org/10.1017/s0033291717000708
58. Krabbe, A., Sikka, P., & Jylkkä, J. (2024). Acceptance as a possible link between past psychedelic experiences and psychological flexibility. *Scientific Reports*, *14*(1). https://doi.org/10.1038/s41598-024-75595-8
59. Krediet, E., Bostoen, T., Breeksema, J., Van Schagen, A., Passie, T., & Vermetten, E. (2020). Reviewing the Potential of Psychedelics for the Treatment of PTSD. *International Journal of Neuropsychopharmacology*, *23*(6), 385. https://doi.org/10.1093/ijnp/pyaa018
60. Kwaśny, A., Wilkowska, A., & Cubała, W. J. (2024). Short-term safety and tolerability profile of 5-methoxy-N,N-dimethyltryptamine in human subjects: a systematic review of clinical trials [Review of *Short-term safety and tolerability profile of 5-methoxy-N,N-dimethyltryptamine in human subjects: a systematic review of clinical trials*]. *Frontiers in Psychiatry*, *15*, 1477996. Frontiers Media. https://doi.org/10.3389/fpsyt.2024.1477996
61. Lawrence, D. W., Carhart-Harris, R., Griffiths, R. R., & Timmermann, C. (2022). Phenomenology and content of the inhaled N, N-dimethyltryptamine (N, N-DMT) experience. *Scientific Reports*, *12*(1). https://doi.org/10.1038/s41598-022-11999-8
62. Lechner-Meichsner, F., Comteße, H., & Olk, M. (2024). Prevalence, comorbidities, and factors associated with prolonged grief disorder, posttraumatic stress disorder and complex posttraumatic stress disorder in refugees: a systematic review [Review of *Prevalence, comorbidities, and factors associated with prolonged grief disorder, posttraumatic stress disorder and complex posttraumatic stress disorder in refugees: a systematic review*]. *Conflict and Health*, *18*(1), 32. BioMed Central. https://doi.org/10.1186/s13031-024-00586-5

63. Lewis, B. R., & Byrne, K. (2023). A Review of MDMA-Assisted Therapy for Posttraumatic Stress Disorder. *Focus*, *21*(3), 247. https://doi.org/10.1176/appi.focus.20220088
64. Li, L., Shen, X., Zeng, G., Huang, H., Chen, Z., Yang, J., Wang, X., Jiang, M., Yang, S., Zhang, Q., & Li, H. (2023). Sexual violence against women remains problematic and highly prevalent around the world [Review of *Sexual violence against women remains problematic and highly prevalent around the world*]. *BMC Women s Health*, *23*(1), 196. BioMed Central. https://doi.org/10.1186/s12905-023-02338-8
65. Lunkenheimer, F., Garatva, P., Steubl, L., & Baumeister, H. (2023). Prevalence and incidence of post-traumatic stress disorder and symptoms in people with chronic somatic diseases: A systematic review and meta-analysis [Review of *Prevalence and incidence of post-traumatic stress disorder and symptoms in people with chronic somatic diseases: A systematic review and meta-analysis*]. *Frontiers in Psychiatry*, *14*, 1107144. Frontiers Media. https://doi.org/10.3389/fpsyt.2023.1107144
66. Mandagere, K., Stoy, S., Hammerle, N., Zapata, I., & Brooks, B. A. (2025). Systematic review and meta-analysis of post-traumatic stress disorder as a risk factor for multiple autoimmune diseases [Review of *Systematic review and meta-analysis of post-traumatic stress disorder as a risk factor for multiple autoimmune diseases*]. *Frontiers in Psychiatry*, *16*, 1523994. Frontiers Media. https://doi.org/10.3389/fpsyt.2025.1523994
67. McGowan, N. M., Rucker, J. J., Yehuda, R., Agrawal, M., Modlin, N. L., Simmons, H., Tofil-Kaluza, A., Das, S., & Goodwin, G. M. (2025). *Investigating the safety and tolerability of single-dose psilocybin for post-traumatic stress disorder: A nonrandomized open-label clinical trial*. https://doi.org/10.1177/02698811251362390
68. Meyer, J. (2013). 3,4-methylenedioxymethamphetamine (MDMA): current perspectives [Review of *3,4-methylenedioxymethamphetamine (MDMA): current perspectives*]. *Substance Abuse and Rehabilitation*, 83. Dove Medical Press. https://doi.org/10.2147/sar.s37258
69. Miller, C. E., & Zoladz, P. R. (2025). Evaluating the potential for psilocybin as a treatment for post-traumatic stress disorder. *The Journal of Pharmacology and Experimental Therapeutics*, *392*(1), 100026. https://doi.org/10.1124/jpet.124.002237
70. Millón, M. B. B., Noguera, L., Bruno, D., Vita, L., Zanino, M., Kassuha, D. E., Ortiz, J. E., Feresin, G. E., Díaz-Dellavalle, P., Orosco, L., Garcés, M. A., Díez, P., Albarracín, S. G., & Bruno, M. A. (2025). Safety and tolerability of multiple sublingual microdoses of 5-MeO-DMT in adults with moderate symptoms of depression and/or anxiety: a randomized, double-blind, placebo-controlled study. *Neuropsychopharmacology*, *50*(11), 1715. https://doi.org/10.1038/s41386-025-02167-3
71. Mion, G., & Villevieille, T. (2013). Ketamine Pharmacology: An Update (Pharmacodynamics and Molecular Aspects, Recent Findings). *CNS Neuroscience & Therapeutics*, *19*(6), 370. https://doi.org/10.1111/cns.12099
72. Mitchell, J., Bogenschutz, M. P., Lilienstein, A., Harrison, C., Kleiman, S. E., Parker-Guilbert, K., G., M. O., Garas, W., Paleos, C., Gorman, I., Nicholas, C. R., Mithoefer, M. C., Carlin, S., Poulter, B., Mithoefer, A. T., Quevedo, S., Wells, G. B., Klaire, S., Kolk, B. van der, … Doblin, R. (2021). MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nature Medicine*, *27*(6), 1025. https://doi.org/10.1038/s41591-021-01336-3
73. Mitchell, J., G., M. O., Kolk, B. van der, Shannon, S., Bogenschutz, M. P., Gelfand, Y., Paleos, C., Nicholas, C. R., Quevedo, S., Balliett, B., Hamilton, S., Mithoefer, M. C., Kleiman, S. E., Parker-Guilbert, K., Tzarfaty, K., Harrison, C., Boer, A. de, Doblin, R., Yazar-Klosinski, B., … Emerson, A. (2023). MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nature Medicine*, *29*(10), 2473. https://doi.org/10.1038/s41591-023-02565-4
74. Moder, J., Sadowska, A., Piasecka, A., Sobiński, A., Miśkiewicz, J., Dudek, A., Pietrusińska, P., Śliwa-Tytko, P., Dziewierz, A., & Kwaśniewska, P. (2025). Post-Traumatic Stress Disorder and its Somatic Comorbidities: A Review [Review of *Post-Traumatic Stress Disorder and its Somatic Comorbidities: A Review*]. *Journal of Education Health and Sport*, *80*, 59387. Kazimierz Wielki University in Bydgoszcz. https://doi.org/10.12775/jehs.2025.80.59387
75. Mohamed, A., Touheed, S., Ahmed, M., Hor, M., & Fatima, S. (2022). The Efficacy of Psychedelic-Assisted Therapy in Managing Post-traumatic Stress Disorder (PTSD): A New Frontier? *Cureus*. https://doi.org/10.7759/cureus.30919
76. Nguyen, K., Mukona, L. T., Nalbandyan, L., Yar, N., Fleur, G. St., Mukona, L., Hernandez, E. W., & Lamberty, N. (2022). Peripartum Complications as Risk Factors for Postpartum Psychosis: A Systemic Review [Review of *Peripartum Complications as Risk Factors for Postpartum Psychosis: A Systemic Review*]. *Cureus*. Cureus, Inc. https://doi.org/10.7759/cureus.29224
77. Nievergelt, C. M., Maihofer, A. X., Atkinson, E. G., Chen, C., Choi, K. W., Coleman, J. R. I., Daskalakis, N. P., Duncan, L. E., Polimanti, R., Aaronson, C. J., Amstadter, A. B., Andersen, S. B., Andreassen, O. A., Arbisi, P. A., Ashley-Koch, A. E., Austin, S. B., Avdibegović, E., Babić, D., Bacanu, S., … Johnson, J. (2023). Discovery of 95 PTSD loci provides insight into genetic architecture and neurobiology of trauma and stress-related disorders. *medRxiv (Cold Spring Harbor Laboratory)*. https://doi.org/10.1101/2023.08.31.23294915
78. Nogueira, M., Golbert, D. F., Menezes, R., Almeida, R. N. de, Coelho, N., Siroký, A., Lima, T., Maia, H., Leão, K. E., & Leão, R. N. (2023). Serotonergic psychedelic 5-MeO-DMT alters plasticity-related gene expression and generates anxiolytic effects in stressed mice. *Research Square (Research Square)*. https://doi.org/10.21203/rs.3.rs-3787978/v1

79. Nowak, A. C., Nutsch, N., Brake, T.-M., Gehrlein, L.-M., & Razum, O. (2023). Associations between postmigration living situation and symptoms of common mental disorders in adult refugees in Europe: updating systematic review from 2015 onwards [Review of *Associations between postmigration living situation and symptoms of common mental disorders in adult refugees in Europe: updating systematic review from 2015 onwards*]. *BMC Public Health*, *23*(1), 1289. BioMed Central. https://doi.org/10.1186/s12889-023-15931-1
80. Omidian, H., & Omidian, A. (2025). The Emergence of Psilocybin in Psychiatry and Neuroscience [Review of *The Emergence of Psilocybin in Psychiatry and Neuroscience*]. *Pharmaceuticals*, *18*(4), 555. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/ph18040555
81. Passie, T. (2018). The early use of MDMA ('Ecstasy') in psychotherapy (1977–1985). *Drug Science Policy and Law*, *4*. https://doi.org/10.1177/2050324518767442
82. Patanè, M., Ghane, S., Karyotaki, E., Cuijpers, P., Schoonmade, L., Tarsitani, L., & Sijbrandij, M. (2022). Prevalence of mental disorders in refugees and asylum seekers: a systematic review and meta-analysis [Review of *Prevalence of mental disorders in refugees and asylum seekers: a systematic review and meta-analysis*]. *Cambridge Prisms Global Mental Health*, *9*, 250. Cambridge University Press. https://doi.org/10.1017/gmh.2022.29
83. Polo-Castellano, C., Álvarez, J. A., Palma, M., Barbero, G. F., Ayuso, J., & Ferreiro-González, M. (2022). Optimization through a Box–Behnken Experimental Design of the Microwave-Assisted Extraction of the Psychoactive Compounds in Hallucinogenic Fungi (Psylocibe cubensis). *Journal of Fungi*, *8*(6), 598. https://doi.org/10.3390/jof8060598
84. Qassem, T., Aly-ElGabry, D., Alzarouni, A., Aziz, K. A., & Arnone, D. (2020). Psychiatric Co-Morbidities in Post-Traumatic Stress Disorder: Detailed Findings from the Adult Psychiatric Morbidity Survey in the English Population. *Psychiatric Quarterly*, *92*(1), 321. https://doi.org/10.1007/s11126-020-09797-4
85. Ragnhildstveit, A., Khan, R., Seli, P., Bass, L. C., August, R. J., Kaiyo, M., Barr, N., Jackson, L. K., Gaffrey, M. S., Barsuglia, J. P., & Averill, L. A. (2023). 5-MeO-DMT for post-traumatic stress disorder: a real-world longitudinal case study. *Frontiers in Psychiatry*, *14*, 1271152. https://doi.org/10.3389/fpsyt.2023.1271152
86. Reckweg, J. T., Mason, N. L., Leeuwen, C. van, Toennes, S. W., Terwey, T. H., & Ramaekers, J. G. (2021). A Phase 1, Dose-Ranging Study to Assess Safety and Psychoactive Effects of a Vaporized 5-Methoxy-N, N-Dimethyltryptamine Formulation (GH001) in Healthy Volunteers. *Frontiers in Pharmacology*, *12*. https://doi.org/10.3389/fphar.2021.760671
87. Reckweg, J. T., Uthaug, M. V., Szabó, A., Davis, A. K., Lancelotta, R., Mason, N. L., & Ramaekers, J. G. (2022). The clinical pharmacology and potential therapeutic applications of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) [Review of *The clinical pharmacology and potential therapeutic applications of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT)*]. *Journal of Neurochemistry*, *162*(1), 128. Wiley. https://doi.org/10.1111/jnc.15587
88. Reddy, A., Patel, S., Barik, A. K., Thappa, P., Jangra, K., Kaur, K., Chauhan, R., & Luthra, A. (2024). The Role of Ketamine in Treatment-resistant Depression: A Narrative Review [Review of *The Role of Ketamine in Treatment-resistant Depression: A Narrative Review*]. *Journal of Exploratory Research in Pharmacology*, 0. https://doi.org/10.14218/jerp.2024.00003
89. Ressler, K. J., Berretta, S., Bolshakov, V. Y., Rosso, I. M., Meloni, E. G., Rauch, S. L., & Carlezon, W. A. (2022). Post-traumatic stress disorder: clinical and translational neuroscience from cells to circuits [Review of *Post-traumatic stress disorder: clinical and translational neuroscience from cells to circuits*]. *Nature Reviews Neurology*, *18*(5), 273. Nature Portfolio. https://doi.org/10.1038/s41582-022-00635-8
90. Rheingold, A. A., Williams, J. L., & Bottomley, J. S. (2024). Prevalence and Co-Occurrence of Psychiatric Conditions Among Bereaved Adults. *JAMA Network Open*, *7*(6). https://doi.org/10.1001/jamanetworkopen.2024.15325
91. Roméo, B., Kervadec, E., Fauvel, B., Strika-Bruneau, L., Amirouche, A., Verroust, V., Piolino, P., & Benyamina, A. (2024). Safety and risk assessment of psychedelic psychotherapy: A meta-analysis and systematic review [Review of *Safety and risk assessment of psychedelic psychotherapy: A meta-analysis and systematic review*]. *Psychiatry Research*, *335*, 115880. Elsevier BV. https://doi.org/10.1016/j.psychres.2024.115880
92. Sarparast, A., Thomas, K., Malcolm, B., & Stauffer, C. S. (2022). Drug-drug interactions between psychiatric medications and MDMA or psilocybin: a systematic review [Review of *Drug-drug interactions between psychiatric medications and MDMA or psilocybin: a systematic review*]. *Psychopharmacology*, *239*(6), 1945. Springer Science+Business Media. https://doi.org/10.1007/s00213-022-06083-y
93. Sbisa, A., Graham, K., Lawrence-Wood, E., McFarlane, A. C., & Toben, C. (2024). PTSD biomarkers: Neuroendocrine signaling to epigenetic variants [Review of *PTSD biomarkers: Neuroendocrine signaling to epigenetic variants*]. *Advances in Clinical Chemistry*. Elsevier BV. https://doi.org/10.1016/bs.acc.2024.06.004
94. Schincariol, A., Orrù, G., Otgaar, H., Sartori, G., & Scarpazza, C. (2024). Posttraumatic stress disorder (PTSD) prevalence: an umbrella review [Review of *Posttraumatic stress disorder (PTSD) prevalence: an umbrella review*]. *Psychological Medicine*, 1. Cambridge University Press. https://doi.org/10.1017/s0033291724002319

95. Schuitmaker, N. (2023). Psilocybin-Assisted Therapy: A scoping review of participants' and facilitators' experiences in qualitative studies [Review of *Psilocybin-Assisted Therapy: A scoping review of participants' and facilitators' experiences in qualitative studies*]. *Research Society and Development*, *12*(9). Grupo de Pesquisa Metodologias em Ensino e Aprendizagem em Ciências. https://doi.org/10.33448/rsd-v12i9.43308
96. Seah, C., Sidamon-Eristoff, A. E., Huckins, L. M., & Brennand, K. (2025). Implications of gene × environment interactions in post-traumatic stress disorder risk and treatment [Review of *Implications of gene × environment interactions in post-traumatic stress disorder risk and treatment*]. *Journal of Clinical Investigation*, *135*(5). American Society for Clinical Investigation. https://doi.org/10.1172/jci185102
97. Sep, M. S. C., Geuze, E., & Joëls, M. (2021). Impaired learning, memory, and extinction in posttraumatic stress disorder: translational meta-analysis of clinical and preclinical studies. *medRxiv (Cold Spring Harbor Laboratory)*. https://doi.org/10.1101/2021.07.19.21260790
98. Sicignano, D. J., Kurschner, R., Weisman, N., Sedensky, A., Hernandez, A. V., & White, C. M. (2024). The Impact of Ketamine for Treatment of Post-Traumatic Stress Disorder: A Systematic Review With Meta-Analyses. *Annals of Pharmacotherapy*, *58*(7), 669. https://doi.org/10.1177/10600280231199666
99. Siddaway, A. P. (2024). Assessment and diagnosis of post-traumatic stress disorders (PTSDs) for medico-legal and other clinical purposes: DSM-5-TR PTSD, ICD-11 PTSD and ICD-11 complex PTSD. *BJPsych Advances*, *30*(6), 383. https://doi.org/10.1192/bja.2024.27
100. Siddaway, A. P. (2025). Flashbacks uniquely characterise post-traumatic stress disorder: distinguishing flashbacks from other psychological processes and phenomena. *BJPsych Advances*, 1. https://doi.org/10.1192/bja.2025.3
101. Sippel, L. M., Hamblen, J. L., Kelmendi, B., Alpert, J. E., Carpenter, L. L., Grzenda, A., Kraguljac, N., McDonald, W. M., Rodriguez, C. I., Widge, A. S., Nemeroff, C. B., Schnurr, P. P., & Holtzheimer, P. E. (2024). Novel Pharmacologic and Other Somatic Treatment Approaches for Posttraumatic Stress Disorder in Adults: State of the Evidence. *American Journal of Psychiatry*, *181*(12), 1045. https://doi.org/10.1176/appi.ajp.20230950
102. Smith, K. W., Sicignano, D. J., Hernández, A. V., & White, C. M. (2021). MDMA-Assisted Psychotherapy for Treatment of Posttraumatic Stress Disorder: A Systematic Review With Meta-Analysis [Review of *MDMA-Assisted Psychotherapy for Treatment of Posttraumatic Stress Disorder: A Systematic Review With Meta-Analysis*]. *The Journal of Clinical Pharmacology*, *62*(4), 463. Wiley. https://doi.org/10.1002/jcph.1995
103. Sottile, R. J., & Vida, T. (2022). A proposed mechanism for the MDMA-mediated extinction of traumatic memories in PTSD patients treated with MDMA-assisted therapy [Review of *A proposed mechanism for the MDMA-mediated extinction of traumatic memories in PTSD patients treated with MDMA-assisted therapy*]. *Frontiers in Psychiatry*, *13*. Frontiers Media. https://doi.org/10.3389/fpsyt.2022.991753
104. Stanicic, F., Zah, V., Grbic, D., Angelo, D. de, & Bibeau, W. S. (2024). Healthcare costs and resource utilization of patients with chronic post-traumatic stress disorder: a retrospective US claims analysis of commercially insured patients. *Journal of Comparative Effectiveness Research*, *13*(12). https://doi.org/10.57264/cer-2024-0058
105. Stavely, C. D. (2025). *EXPLORING IBOGAINE/5-MEO-DMT AS TREATMENT FOR THE RELIEF OF PTSD SYMPTOMS IN VETERANS*. https://www.centreforevidence.org/article/20250608-exploring-ibogaine-5-meo-dmt-as-treatment-for-the-relief-of-ptsd-symptoms-in-veterans
106. Stocker, K., & Liechti, M. E. (2024). Methylenedioxymethamphetamine is a connectogen with empathogenic, entactogenic, and still further connective properties: It is time to reconcile "the great entactogen—empathogen debate" [Review of *Methylenedioxymethamphetamine is a connectogen with empathogenic, entactogenic, and still further connective properties: It is time to reconcile "the great entactogen—empathogen debate"*]. *Journal of Psychopharmacology*, *38*(8), 685. SAGE Publishing. https://doi.org/10.1177/02698811241265352
107. Straumann, I., Holze, F., Becker, A., Ley, L., Halter, N., & Liechti, M. E. (2024). Safety pharmacology of acute psilocybin administration in healthy participants. *Neuroscience Applied*, *3*, 104060. https://doi.org/10.1016/j.nsa.2024.104060
108. Straumann, I., Vizeli, P., Avedisian, I., Erne, L., Noorshams, D., Vukalović, I., Eckert, A., Luethi, D., Rudin, D., & Liechti, M. E. (2025). Acute effects of MDMA, MDA, lysine-MDMA, and lysine-MDA in a randomized, double-blind, placebo-controlled, crossover trial in healthy participants. *Neuropsychopharmacology*. https://doi.org/10.1038/s41386-025-02248-3
109. Strauss, D., Ghosh, S., Murray, Z., & Gryzenhout, M. (2022). An Overview on the Taxonomy, Phylogenetics and Ecology of the Psychedelic Genera Psilocybe, Panaeolus, Pluteus and Gymnopilus. *Frontiers in Forests and Global Change*, *5*. https://doi.org/10.3389/ffgc.2022.813998
110. Suliman, S., Heuvel, L. L. van den, Bröcker, E., & Seedat, S. (2025). Neurocognitive difficulties in trauma-exposed adults with metabolic syndrome: no influence of PTSD status or PTSD and metabolic syndrome comorbidity. *Discover Mental Health*, *5*(1). https://doi.org/10.1007/s44192-025-00141-5
111. Swainson, J., Klassen, L. J., Brennan, S., Chokka, P., Katzman, M. A., Tanguay, R. L., & Khullar, A. (2022). Non-parenteral Ketamine for Depression: A Practical Discussion on Addiction Potential and Recommendations for Judicious Prescribing. *CNS Drugs*, *36*(3), 239. https://doi.org/10.1007/s40263-022-00897-2

112. Tedesco, S., Gajaram, G., Chida, S., Ahmad, A., Pentak, M., Kelada, M., Lewis, L., Krishnan, D., Tran, C., Soetan, O. T., Mukona, L. T., & Jolayemi, A. (2021). The Efficacy of MDMA (3,4-Methylenedioxymethamphetamine) for Post-traumatic Stress Disorder in Humans: A Systematic Review and Meta-Analysis. *Cureus*. https://doi.org/10.7759/cureus.15070
113. Tedla, A., Asnakew, S., Legas, G., Munie, B. M., Tareke, M., & Beka, M. (2024). Post-traumatic stress disorder among military personnel admitted at the Northwest Command Level Three Military Hospital, Bahir Dar, Ethiopia, 2022: an institution-based cross-sectional study. *Frontiers in Psychiatry*, *15*. https://doi.org/10.3389/fpsyt.2024.1410630
114. Topel, M., & Ciccone, D. (2025). Ketamine Assisted EMDR Therapy™ for PTSD: investigating the synergistic effects of pharmacotherapy and psychotherapy. *European Journal of Psychotraumatology*, *16*(1), 2572861. https://doi.org/10.1080/20008066.2025.2572861
115. Torres-Berrío, A., & Nava-Mesa, M. O. (2018). The opioid system in stress-induced memory disorders: From basic mechanisms to clinical implications in post-traumatic stress disorder and Alzheimer's disease [Review of *The opioid system in stress-induced memory disorders: From basic mechanisms to clinical implications in post-traumatic stress disorder and Alzheimer's disease*]. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *88*, 327. Elsevier BV. https://doi.org/10.1016/j.pnpbp.2018.08.011
116. Tran, K., & MacDougall, D. (2024). Ketamine for Adults With Substance Use Disorders. *Canadian Journal of Health Technologies*, *4*(2). https://doi.org/10.51731/cjht.2024.845
117. Turkia, M. (2024). *5-MeO-DMT in the complete resolution of the consequences of chronic, severe sexual abuse in early childhood—a retrospective case study*. https://doi.org/10.31234/osf.io/bvk2f
118. Underwood, M. (2025). *THE USE OF IBOGAINE IN THE TREATMENT OF SUBSTANCE USE DISORDERS: INTEGRATING PSYCHOACTIVE EXPERIENCES AS PART OF THE RECOVERY JOURNEY*. https://repository.canterbury.ac.uk/item/9vzv2/the-use-of-ibogaine-in-the-treatment-of-substance-use-disorders-integrating-psychoactive-experience-as-part-of-the-recovery-journey
119. Uthaug, M. V., Lancelotta, R., Oorsouw, K. van, Kuypers, K. P. C., Mason, N. L., Rak, J., Šuláková, A., Jurok, R., Maryška, M., Kuchař, M., Páleníček, T., Riba, J., & Ramaekers, J. G. (2019). A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms. *Psychopharmacology*, *236*(9), 2653. https://doi.org/10.1007/s00213-019-05236-w
120. Van Der Kolk, B. A., Wang, J. B., Yehuda, R., Bedrosian, L., Coker, A. R., Harrison, C., Mithoefer, M., Yazar-Klosinki, B., Emerson, A., Doblin, R., & Moitra, E. (2024). Effects of MDMA-assisted therapy for PTSD on self-experience. *PLOS ONE*, *19*(1). https://doi.org/10.1371/journal.pone.0295926
121. Varker, T., Watson, L., Gibson, K., Forbes, D., & O'Donnell, M. L. (2021). Efficacy of Psychoactive Drugs for the Treatment of Posttraumatic Stress Disorder: A Systematic Review of MDMA, Ketamine, LSD and Psilocybin. *Journal of Psychoactive Drugs*, *53*(1), 85. https://doi.org/10.1080/02791072.2020.1817639
122. Vliet, N. I. van, Stant, A. D., Huntjens, R. J. C., Dijk, M. K. van, & Jongh, A. de. (2024). Cost-effectiveness analysis of the treatment of posttraumatic stress disorder related to childhood abuse: comparison of phase-based treatment and direct trauma-focused treatment. *Frontiers in Psychology*, *15*. https://doi.org/10.3389/fpsyg.2024.1310372
123. Vorobyeva, N. S., & Kozlova, A. A. (2022). Three Naturally-Occurring Psychedelics and Their Significance in the Treatment of Mental Health Disorders [Review of *Three Naturally-Occurring Psychedelics and Their Significance in the Treatment of Mental Health Disorders*]. *Frontiers in Pharmacology*, *13*. Frontiers Media. https://doi.org/10.3389/fphar.2022.927984
124. Wahba, M., Hayes, C., Kletter, M., & McAllister-Williams, R. H. (2024). Worsening suicidal ideation and prolonged adverse event following psilocybin administration in a clinical setting: case report and thematic analysis of one participant's experience. *BJPsych Open*, *10*(6). https://doi.org/10.1192/bjo.2024.768
125. Wang, Y., Liu, L., Wang, J., Li, J., Li, H., Wang, R., Wang, H., Wang, M., Liu, Q., Fan, Z., Zhang, Y., Zhang, X., Wang, D., Wang, S., Xue, R., Mao, J., Cai, M., Wei, P., Dong, H., … Zhao, G. (2025). Time-Dependent Therapeutic Effect of *S* -Ketamine on PTSD Mediated by VTA-OFC Dopaminergic Neurocircuit. *Advanced Science*. https://doi.org/10.1002/advs.202500805
126. Wild, J., Duffy, M., & Ehlers, A. (2023). Moving forward with the loss of a loved one: treating PTSD following traumatic bereavement with cognitive therapy. *The Cognitive Behaviour Therapist*, *16*. https://doi.org/10.1017/s1754470x23000041
127. Wojtas, A. (2023). The possible place for psychedelics in pharmacotherapy of mental disorders [Review of *The possible place for psychedelics in pharmacotherapy of mental disorders*]. *Pharmacological Reports*, *75*(6), 1313. Elsevier BV. https://doi.org/10.1007/s43440-023-00550-9
128. Wolfgang, A., Fonzo, G. A., Gray, J. C., Krystal, J. H., Grzenda, A., Widge, A. S., Kraguljac, N. V., McDonald, W. M., Rodríguez, C. I., & Nemeroff, C. B. (2025). MDMA and MDMA-Assisted Therapy [Review of *MDMA and MDMA-Assisted Therapy*]. *American Journal of Psychiatry*, *182*(1), 79. American Psychiatric Association. https://doi.org/10.1176/appi.ajp.20230681

129. Yerubandi, A., Thomas, J. E., Bhuiya, N. M. M. A., Harrington, C., Villa Zapata, L., & Caballero, J. (2024). Acute Adverse Effects of Therapeutic Doses of Psilocybin: A Systematic Review and Meta-Analysis. *JAMA Network Open*, *7*(4). https://doi.org/10.1001/jamanetworkopen.2024.5960
130. Yockey, R. A. (2025). Reconsidering Ibogaine for the treatment of severe mental illness and substance use disorders. *Journal of Medicine, Surgery, and Public Health*, *7*, 100213. https://doi.org/10.1016/j.glmedi.2025.100213
131. Zeifman, R. J., Kettner, H., Ross, S., Weiss, B., Mithoefer, M. C., Mithoefer, A. T., & Wagner, A. C. (2024). Preliminary evidence for the importance of therapeutic alliance in MDMA-assisted psychotherapy for posttraumatic stress disorder. *European Journal of Psychotraumatology*, *15*(1), 2297536. https://doi.org/10.1080/20008066.2023.2297536