

PTSD Treatment is Evolving. Could Psychedelic- Assisted Therapy Help Close the Gap?

Samantha Gorun, MREs - Associate Research Scientist
Johnny Zhou, PharmD - Associate Research Scientist

PTSD Treatment is Evolving. Could Psychedelic-Assisted Therapy Help Close the Gap?

Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder that develops following a traumatic event.¹ Despite the availability of several psychotherapeutic approaches, many people with PTSD do not achieve clinically significant symptom improvement. Furthermore, although medications may be used alongside psychotherapy, augmenting psychotherapy with existing medications is generally not more effective than psychotherapy alone.^{2,3} This treatment gap has prompted researchers to explore new therapeutic approaches, including psychedelic-assisted therapy (PAT) and psychedelic-adjacent therapy. Once considered a fringe area of research, compounds such as 3,4-methylenedioxymethamphetamine (MDMA), ketamine, psilocybin, and cannabinoids are now being investigated for their potential to improve outcomes for people living with PTSD.^{2,3}

This post reviews the symptoms, burden, and treatment landscape of PTSD, summarizes the clinical rationale and empirical evidence for various classes of psychedelic-assisted and psychedelic-adjacent therapy, and discusses key challenges and priorities for future research.

Defining PTSD

PTSD is one of the most debilitating psychiatric conditions in routine care. It arises after direct or indirect exposure to physical or emotional traumatic events such as military combat or war, sexual or other physical violence, natural disaster, or severe injury or illness. PTSD is characterized by four interrelated symptom clusters: (1) intrusive re-experiencing (including unwanted memories, nightmares, flashbacks, and intense distress when reminded of the trauma); (2) persistent avoidance of trauma-related thoughts, feelings, conversations, places, or activities; (3) negative alterations in cognition and mood (including persistent guilt, shame, distorted blame, emotional numbing, and anhedonia); and (4) marked alterations in arousal and reactivity (including hypervigilance, exaggerated startle, irritability or anger, sleep disturbance, concentration problems, and reckless or self-destructive behavior).^{1,4,5} To meet DSM-5-TR criteria, these symptoms must last at least one month and cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.⁴⁻⁶

The Ongoing Burden of PTSD

PTSD can have profound impacts on an individual's mental health, relationships, employment, daily functioning, and quality of life (QoL), which manifest in higher rates of comorbid mental illness, lower work and family functioning and satisfaction, higher rates of suicide attempts and death by suicide, and impaired mobility and self-care.¹ Additionally, people with PTSD may delay access to treatment for fear of being identified as mentally ill and "dangerous/violent" or "crazy."⁷

PTSD also comes with substantial societal burden. In the United States alone, the excess economic burden of PTSD was estimated at more than \$230 billion annually.⁸ Globally, around 4% of people are expected to experience PTSD during their lifetime.¹

Why Current Treatments are Not Always Enough

Current clinical guidelines consistently recommend trauma-focused psychotherapies, including cognitive behavioural therapy (CBT), prolonged exposure therapy, and eye movement desensitization and reprocessing (EMDR), as first-line treatments for PTSD—see **Table 1** for a summary of which treatment modalities are recommended by four major clinical bodies.^{1,9}

However, research suggests that as many as 50% of patients may fail to achieve clinically meaningful improvement.¹ When remission is not achieved with psychotherapy alone, augmentation with medication can be considered. However, currently approved medications often produce relatively low remission rates of 20% to 30%. This unmet need has motivated researchers to investigate whether novel therapies could enhance existing treatment approaches.

Table 1: Therapy recommendations by professional body

	APA	NICE	APS	VA/DoD
CBT + PE	Strong	Strong	Strong	Strong
EMDR	Conditional	Conditional	Strong	Strong
Brief psychodynamic	Conditional	None	None	None
Humanistic	None	None	Conditional	Conditional
Polyvagal	None	None	None	None
Pharmacotherapy	Conditional	Conditional	Conditional	Conditional

Note: Adapted from Kowalski et al. (2024).⁹

Abbreviations: APA, American Psychological Association; APS, Australian Psychological Society; CBT, Cognitive Behavioural Therapy; DoD, Department of Defense; EMDR, Eye Movement Desensitization and Reprocessing; NICE, National Institute for Health and Care Excellence; PE, Prolonged Exposure; VA, Veterans Affairs.

A New Generation of Therapies

Psychedelic-assisted therapy is often misunderstood to be a substitute for psychotherapy. In reality, researchers are exploring whether certain compounds can help patients engage more effectively in psychotherapy by promoting emotional openness, reducing fear responses, or increasing neuroplasticity.^{2,3} The following sections summarize the principal compounds being studied as psychedelic-assisted or related therapies.

3,4-methylenedioxymethamphetamine (MDMA)

Two landmark Phase III clinical trials, MAPP1 and MAPP2, found that patients receiving MDMA-assisted therapy experienced significantly greater reductions in PTSD symptom severity and disability compared with participants receiving psychotherapy and placebo.^{11,12} In MAPP1 and MAPP2, 67% and 71% of patients in the MDMA-assisted therapy group no longer met diagnostic criteria for PTSD at the primary study endpoint, compared with 32% and 48% in their respective placebo groups.

Psilocybin and Other Classical Psychedelics

Psilocybin and other classical psychedelics such as lysergic acid diethylamide (LSD) and dimethyltryptamine (DMT) primarily act through serotonin 5-HT_{2A} receptors and may also promote neuroplasticity and emotional processing.^{2,3} Research remains in its early stages, but preliminary findings are encouraging. In a recent Phase II study, of 12 participants who received psilocybin-assisted therapy 9 (75%) achieved remission and 10 (83%) experienced a clinically meaningful response.¹⁶ However, this study was limited by the fact that it recruited a small sample of 12 patients, did not include a control group, and did not implement blinding. As such, larger controlled trials are still needed before definitive conclusions can be drawn.

Ketamine

Ketamine is classified as a dissociative anaesthetic and is sometimes described as “psychedelic-adjacent.” Ketamine has attracted growing interest because of its effects on neuroplasticity, learning, and memory.^{13,14} By influencing glutamate signalling and brain-derived neurotrophic factor, ketamine may help create conditions that support fear extinction and memory reconsolidation when combined with psychotherapy.

A recent meta-analysis found significant improvements in PTSD symptom scores among patients treated with ketamine, although the evidence base is limited by methodological variability across studies and the absence of robust placebo-controlled data.¹⁵

Related Emerging Treatments

Cannabinoids are not strictly psychedelics, but like psychedelics they have the capacity to induce an altered sense of self and have been explored as potential treatments for PTSD.² Some researchers have proposed that dysfunction in the endocannabinoid system may contribute to symptoms such as hyperarousal, insomnia, and recurring nightmares, and therefore that cannabinoids might temporarily relieve symptoms.^{2,17} Evidence remains limited, but one clinical trial found that nabilone, a synthetic cannabinoid, significantly reduced trauma-related nightmares among military personnel living with PTSD.¹⁸

Directions for Future Research

To gain reimbursement and formulary support, PAT will need to demonstrate more than short-term clinical effectiveness. Existing studies of PAT have been constrained by short follow-up duration, and subsequent studies will need to demonstrate durable efficacy given that PTSD can persist for years.¹

Additionally, decision-makers increasingly look for evidence showing that a treatment improves patients' QoL in a way that justifies its cost. Future clinical trials should therefore capture QoL outcomes alongside symptom measures, enabling researchers to estimate long-term patient benefits and overall value. By combining these outcomes with detailed treatment costs, economic evaluations can compare PAT with current treatment options, including psychotherapy and pharmacotherapy. These analyses will be critical for understanding whether PAT represents a cost-effective addition to existing care pathways, particularly for patients who have not responded to first- or second-line treatments.

Clinical studies of PAT for PTSD report a range of symptom-based and other PROs, but they do not consistently include generic preference-based measures of health-related QoL, such as the EQ-5D. Although the SF-36 is not itself preference-based, responses can be converted into SF-6D utility values. Utility-based measures of QoL can be used to calculate quality-adjusted life years and are important for health technology assessment and reimbursement submissions. These measures should be incorporated into future trials.

Challenges

Despite the excitement surrounding PAT, several barriers to approval and adoption remain.

One challenge is the difficulty of maintaining blinding in clinical trials. Because psychedelic compounds produce noticeable psychological effects, participants can often determine whether they received the active treatment. In the MAPP1 study, approximately 90% of participants receiving MDMA correctly guessed their treatment assignment, raising concerns about expectancy effects.^{3,11,12} Expectancy effects occur when participants identify which arm they were assigned to and anticipate either symptom alleviation or worsening, leading to placebo and nocebo effects, respectively.¹⁹

Accessibility also remains a concern. PAT often involves extensive preparation, supervised dosing sessions, and follow-up psychotherapy, making it both time-intensive and potentially expensive. These barriers may disproportionately affect low-income populations at elevated risk of PTSD.³ Furthermore, uptake of PAT may be constrained by lack of training, treatment duration, undesired hallucinogenic effects and familiarity among prescribers.²⁰

Lastly, because psychedelics are prohibited in many jurisdictions, stigma may discourage patients from seeking PAT. In a survey of 21 service members and veterans with PTSD and a history of traumatic brain injury, fear of workplace consequences (29%) and fear of judgement (24%) were common social barriers to use of psychedelics.²¹ However, after reading a brief psychoeducation about PAT, participants' attitudes toward PAT were significantly more positive than they were at baseline.

Looking Ahead

Psychedelics are not replacing psychotherapy. Rather, researchers are exploring whether these compounds can become valuable tools within evidence-based treatment to improve the effects of psychotherapy, helping more people move toward recovery after trauma.^{2,3}

The growing interest in PAT reflects an important reality: many people living with PTSD still need better treatment options. Current evidence suggests that certain psychedelic compounds may help patients engage more effectively in psychotherapy and potentially achieve outcomes that have been difficult to attain through conventional approaches alone. Among the therapies currently under investigation, MDMA has demonstrated the strongest clinical evidence, while ketamine, psilocybin, and cannabinoid-based therapies continue to show promise, but their effects are not well documented.^{11,12,15,16}

Regulators, researchers, and other stakeholders should ensure that clinical trials are designed to assess the efficacy, safety, and long-term effects of PAT. Trials should also evaluate QoL outcomes to provide a more comprehensive understanding of the patient journey during PAT. In addition, guidance is needed on appropriate treatment duration and stopping rules for PAT.

Despite these uncertainties, PAT is a promising treatment modality that, if approved, could represent the first major innovation in the pharmacological treatment of PTSD since sertraline and paroxetine were approved for PTSD by the United States Food and Drug Administration in 1999 and 2001, respectively. For patients who have not benefited from conventional treatments, PAT may therefore offer a much-needed new therapeutic option and renewed hope for recovery.

References

1. Ressler KJ, Rothbaum BO, Schnurr PP, et al. Post-traumatic stress disorder. *Nature Reviews Disease Primers*. 2026;12(1):27.
2. Krediet E, Bostoen T, Brecksema J, van Schagen A, Passie T, Vermetten E. Reviewing the Potential of Psychedelics for the Treatment of PTSD. *The international journal of neuropsychopharmacology*. 2020;23(6):385-400.
3. Zaretsky TG, Jagodnik KM, Barsic R, et al. The Psychedelic Future of Post-Traumatic Stress Disorder Treatment. *Current neuropharmacology*. 2024;22(4):636-735.
4. Association AP. *Diagnostic and Statistical Manual of Mental Disorders*. 5 ed: American Psychiatric Association Publishing; 2022.
5. Barnhill JW. Posttraumatic Stress Disorder (PTSD). 2026; <https://www.msmanuals.com/professional/psychiatric-disorders/anxiety-and-trauma-and-stressor-related-disorders/posttraumatic-stress-disorder-ptsd>, 2026.
6. Siddaway AP. 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*. 2024;30(6):383-397.
7. Mittal D, Drummond KL, Blevins D, Curran G, Corrigan P, Sullivan G. Stigma associated with PTSD: perceptions of treatment seeking combat veterans. *Psychiatric rehabilitation journal*. 2013;36(2):86-92.
8. Davis LL, Schein J, Cloutier M, et al. The Economic Burden of Posttraumatic Stress Disorder in the United States From a Societal Perspective. *The Journal of clinical psychiatry*. 2022;83(3).
9. Kowalski J, Elżanowski A, Śliwerski A. A review of selected psychotherapies for PTSD, their efficacy and treatment guidelines in adults. *Psychiatria polska*. 2024;58(2):315-328.
10. O'Brien S, Nutt D. MDMA-assisted therapy: challenges, clinical trials, and the future of MDMA in treating behavioral disorders. *CNS spectrums*. 2025;30(1):e15.
11. Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-Assisted Therapy for Severe PTSD: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study. *Focus (American Psychiatric Publishing)*. 2023;21(3):315-328.
12. Mitchell JM, Ot'alora GM, van der Kolk B, et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nature medicine*. 2023;29(10):2473-2480.
13. Wellington NJ, Boqcas AP, Lagopoulos J, Quigley BL, Kuballa AV. Molecular pathways of ketamine: A systematic review of immediate and sustained effects on PTSD. *Psychopharmacology*. 2025;242(6):1197-1243.
14. Malik MA, Halasa M, Chia J, et al. The impact of ketamine on posttraumatic stress disorder (PTSD) symptomatology in trauma-exposed populations: a narrative review. *Journal of trauma and injury*. 2026;39(2):119-127.
15. Almeida TM, Lacerda da Silva UR, Pires JP, et al. Effectiveness of Ketamine for the Treatment of Post-Traumatic Stress Disorder - A Systematic Review and Meta-Analysis. *Clinical neuropsychiatry*. 2024;21(1):22-31.
16. Armstrong SB, Levin AW, Sepeda ND, et al. Safety, feasibility, and preliminary clinical outcomes of psilocybin-assisted therapy for veterans with severe, treatment-resistant PTSD: an open-label pilot clinical trial. *Communications Medicine*. 2026;6(1):411.
17. Abizaid A, Merali Z, Anisman H. Cannabis: A potential efficacious intervention for PTSD or simply snake oil? *Journal of Psychiatry and Neuroscience*. 2019;44(2):75-78.
18. Jetly R, Heber A, Fraser G, Boisvert D. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology*. 2015;51:585-588.
19. Flaming LJ, Aday JS, van Elk M. Expectancy Effects Cannot Be Neglected in MDMA-Assisted Therapy Research. *ACS chemical neuroscience*. 2023;14(23):4062-4063.
20. Medlinskiene K, Tomlinson J, Marques I, Richardson S, Stirling K, Petty D. Barriers and facilitators to the uptake of new medicines into clinical practice: a systematic review. *BMC health services research*. 2021;21(1):1198.
21. Gray JC, Murphy M, Carter SE, et al. Beliefs and Perceived Barriers Regarding Psychedelic-assisted Therapy in a Pilot Study of Service Members and Veterans With a History of Traumatic Brain Injury. *Military medicine*. 2023;188(11-12):e3356-e3362.