DOI: https://doi.org/10.4038/jdrra.v3i2.87

The Journal of Desk Research Review and Analysis, Vol. 3, Issue 2, 2025, 74 - 79

PSYCHEDELIC-ASSISTED THERAPY (PAT): A NEW FRONTIER IN MENTAL HEALTH TREATMENT

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Abstract

Psychedelic-assisted therapy (PAT) has emerged as a promising and innovative approach to treating a range of mental health disorders, including depression, post-traumatic stress disorder (PTSD), and substance use disorders. Once sidelined due to regulatory bans and social stigma, psychedelics such as psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), and ketamine are now the focus of rigorous clinical investigation. This review explores the mechanisms of action, therapeutic applications, clinical evidence, ethical considerations, and future directions for psychedelic-assisted therapies. Although the general concepts of PAT are well described in literature, this paper highlights emerging evidence from recent trials (2020–2024), discusses ongoing debates on safety and regulation, and identifies underexplored populations such as older adults. Thus, this review contributes a contemporary synthesis focusing on evidence gaps and future research priorities.

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Received date: 27.05.2025 Accepted date: 23.07.2025

Print Publishing Date: 31.10.2025 Web Publishing Date: 31.10.2025

Introduction

Psychedelic substances have been utilised for centuries in traditional ceremonies and healing practices among indigenous cultures. In the 1950s and 1960s, Western scientists explored their therapeutic potential, but the prohibitionist policies of the late 20th century halted much of this research (Nichols, 2016). Recently, a resurgence of interest, often referred to as the "Psychedelic Renaissance," has brought these compounds back into clinical and scientific focus, offering hope for treatment-resistant psychiatric conditions.

Psychedelic substances used in PAT are typically administered by trained clinicians under controlled settings, rather than being self-administered by patients. The therapeutic model emphasizes medical supervision, psychological support, and ethical care throughout treatment (Daniel et al., 2024).

Mechanisms of Action

Psychedelics primarily exert their effects by acting as agonists at the serotonin 5-HT2A receptor, leading to altered perception, mood, and cognition (Vollenweider & Preller, 2020). Functional MRI studies have shown that psychedelics disrupt the activity of the Default Mode Network (DMN), a brain network associated with self-referential thought and rumination (Carhart-Harris et al., 2012). By reducing DMN coherence, psychedelics facilitate a “resetting” of rigid neural circuits implicated in depression and PTSD. Additionally, psychedelics promote neuroplasticity, increasing dendritic growth and synaptic density, which may underlie long-term therapeutic benefits.

Beyond these three core mechanisms, other pathways have been proposed. For example, studies suggest alterations in glutamate transmission, modulation of brain entropy, and increased thalamocortical connectivity may contribute to enhanced emotional processing and cognitive flexibility (Carhart-Harris et al., 2021; Barrett et al., 2020). Further exploration of these mechanisms remains an active area of research.

Key Psychedelics in Therapeutic Use

Psychedelic-assisted therapy typically follows a structured approach involving three key stages. The first stage is preparation, where patients are carefully screened and prepared psychologically for the psychedelic experience. In the dosing session, which is the second stage, the psychedelic is administered in a controlled, supportive environment with trained therapists present. In the last or the third stage – integration, post-experience therapy sessions help patients process and integrate insights from the experience into daily life. The therapeutic model emphasises the importance of "set and setting," recognising that the patient's mindset and the physical and social environment critically shape outcomes (Johnson et al., 2008).

Synthetic compounds such as LSD, MDMA, and 2-(2-Chlorophenyl)-2-(methylamino) cyclohexanone (ketamine), alongside naturally occurring alkaloids like 4-phosphoryloxy-N, N-dimethyltryptamine (psilocybin, found in numerous Psilocybe mushroom species) and 12-Methoxyibogamine (ibogaine, derived from Tabernanthe iboga), have been utilised in various studies and Phase 2 clinical trials. These compounds are orally bioactive yet possess distinct modes of action (Schenberg, 2018).

LSD (lysergic acid diethylamide) was among the first psychedelics explored for psychiatric use. Although trials are limited for LSD recently, a meta-analysis with strong research from 60 years ago confirmed LSD has significant potential for alcohol use disorders (Krebs and Johansen, 2012). Further recent studies suggest it might help alleviate anxiety associated with life-threatening diseases and

reduce symptoms of alcoholism, though research is less advanced compared to psilocybin and MDMA (Gasser et al., 2014).

Psilocybin, the active ingredient in certain species of mushrooms, has demonstrated efficacy in treating major depressive disorder and end-of-life anxiety. Studies have reported rapid and sustained antidepressant effects following just one or two doses combined with psychotherapy (Davis et al., 2021). The safety ratio is remarkably high, and even in unsupervised settings, the risk profile is reported low (Gable, 2004; Nutt et al., 2010; Tylš et al., 2014; van Amsterdam et al., 2011).

Originally synthesised in the early 20th century, MDMA has shown particular promise in treating PTSD. By increasing emotional openness and reducing fear responses, MDMA enhances the therapeutic process during exposure therapy. The Multidisciplinary Association for Psychedelic Studies (MAPS) Phase III trials demonstrated that MDMA-assisted therapy led to significant symptom reduction in PTSD patients (Mitchell et al., 2021). When measured by clinician-observed results, patient self-report outcomes, and dropout rates, MDMA-assisted psychotherapy outperformed longer exposure, according to an independent exploratory meta-analysis (Amoroso and Workman, 2016).

Ketamine is the most studied substance, which in higher doses is an anaesthetic in use for decades and at lower dosages, it momentarily alters consciousness, causing mood and cognitive shifts (Mion, 2017). Although technically a dissociative anaesthetic rather than a classical psychedelic, ketamine and its derivative esketamine have been approved for treatment-resistant depression. Ketamine acts on the glutamatergic NMDA receptor, promoting rapid antidepressant effects (Berman et al., 2000).

Ayahuasca, a traditional Amazonian brew containing DMT, is being explored for its potential in treating substance use disorders and depression. Early studies indicate promising results, though larger clinical trials are needed (Palhano-Fontes et al., 2019). Finally, ibogaine is the least developed psychedelic in the channel. Since the National Institute on Drug Abuse (NIDA) cancelled efforts to produce this molecule to treat opioid addiction in the 1990s, no interventional clinical trials have been conducted or registered (Alper, 2001). Given that ibogaine can lengthen the QT interval (Koenig and Hilber, 2015) and may lead to potentially deadly cardiac arrhythmias (Koenig et al., 2014), there are significant safety concerns. This significantly alters the safety profile of ibogaine in comparison to other psychedelics.
To enhance clarity, a table is included summarising key psychedelics, mechanisms, efficacy, and therapeutic indications.

Table 01. Summary of Key Psychedelic Substances: Mechanisms, Therapeutic Indications and Evidence Levels

Substance	Primary Mechanism	Key Indications	Evidence Level
LSD	5-HT2A agonist, DMN modulation	Alcohol dependence, anxiety in terminal illness	Moderate (historical + small RCTs)
Psilocybin	5-HT2A agonist, neuroplasticity	Major depression, end-of-life anxiety, PTSD	High (Phase II/III trials)
MDMA	Monoamine release, amygdala desensitization	PTSD, anxiety	High (Phase III trials)
Ketamine	NMDA receptor antagonist	Treatment-resistant depression	High (approved therapy)
Ayahuasca	DMT-mediated serotonergic modulation	Substance use, depression	Moderate (open-label)
Ibogaine	Kappa-opioid and NMDA modulation	Opioid dependence	Low (preclinical + anecdotal)

Clinical Evidence

Clinical trials have provided solid evidence supporting the efficacy of psychedelic-assisted therapies. In a randomized clinical trial, psilocybin therapy led to a 71% response rate and a 54% remission rate in major depressive disorder after just two sessions (Davis et al., 2021). MDMA-assisted therapy for PTSD showed that 67% of participants no longer met criteria for PTSD after treatment, compared to 32% in the placebo group (Mitchell et al., 2021). Open-label studies with ayahuasca have shown reductions in depression and anxiety symptoms within hours of administration, with sustained effects over weeks (Palhano-Fontes et al., 2019). These outcomes, combined with relatively favourable safety profiles under clinical supervision, have led regulatory bodies such as the U.S. FDA to grant Breakthrough Therapy Designations to psilocybin and MDMA treatments.

Although general depression rates tend to decline with age, many older individuals still experience significant psychological distress that often goes underreported due to variations in depression, anxiety and PTSD presentation. Standard treatments like serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants like mirtazapine are commonly prescribed but take weeks to work, can cause various side effects, and show only moderate effectiveness in this age group. Despite limited research, a recent meta-analysis findings indicate that psychedelic-assisted therapy may be both safe and well tolerated in older populations. And they recommend more research into its potential benefits for older adults (Bouchet, 2024).

The way adverse events (AEs) are evaluated and reported in psychedelic-assisted therapies lacks consistency and may not fully suit the unique nature of these treatments. Although standard clinical trial methods for assessing harm are sometimes used in PAT research, two key aspects call for more tailored approaches: PATs combine both drug treatment and psychotherapy, and the experiences they induce are deeply impactful and unique. Palitsky and colleagues proposed a framework to better assess AEs following treatment, considering both the drug and therapy aspects, as well as the significant changes in spirituality and worldview that psychedelics can cause. They emphasise that as the field of psychedelic therapy advances, accurate and thorough assessment of these specific AEs is essential for reducing patient risks and understanding the true benefits and risks of the treatments (Palitsky et al, 2024).

Ethical and Regulatory Considerations

Ethical considerations in PAT include informed consent, management of vulnerability during altered states, and respect for indigenous knowledge systems (Tupper et al., 2015). Empirical research also supports the value of therapist experiential training in psychedelics, enhancing empathy and therapeutic alliance (Earleywine et al., 2023). However, training models remain debated, with calls for global ethical guidelines.

Regulatory developments are progressing: Australia and Canada have begun limited clinical use approvals for psilocybin and MDMA, while the U.S. Food and Drug Administration (FDA) anticipates full approval by 2025 (Carhart-Harris et al., 2021). Continued collaboration between policymakers, ethicists, and clinicians will be key to safe and equitable access.

Future Directions

Several exciting developments are shaping the future of psychedelic therapy. Microdosing, which involves administering sub-perceptual doses of psychedelics, is being explored for mood and cognitive enhancement, although clinical evidence remains limited (Kuypers et al., 2019). Researchers are developing compounds that retain therapeutic benefits without inducing hallucinations, potentially

broadening the clinical utility of non-hallucinogenic psychedelics. Virtual reality and digital therapeutics are vital future concerns which may enhance the preparation and integration phases. Studies have been commenced to explore psychedelics for conditions such as Alzheimer's disease, eating disorders, and obsessive-compulsive disorder. As psychedelic science advances, multidisciplinary collaboration among clinicians, neuroscientists, ethicists, and policymakers will be essential to realise the full potential of these treatments responsibly.

Conclusion

Psychedelic-assisted therapy represents a paradigm shift in mental health treatment, offering profound therapeutic potential for conditions historically resistant to conventional therapies. Although challenges remain, careful scientific exploration, ethical vigilance, and patient-centred approaches can ensure that psychedelics fulfil their promise as powerful tools for healing.

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