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Psychedelics in psychiatric treatment: a literature review

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Abstract
Background: Psychedelic substances have been used for millennia in religious and healing contexts and have recently re-emerged as subjects of scientific interest due to advances in neuroscience and psychiatry. Research suggests that psychedelics may address limitations of conventional psychiatric treatments, particularly in disorders such as major depressive disorder, PTSD, substance use disorders, and anxiety disorders.
Aim: This article aims to critically review and synthesize current evidence on the neurobiological mechanisms, therapeutic efficacy, and safety profiles of selected psychedelic substances—psilocybin, LSD, MDMA, and ketamine—in the treatment of psychiatric disorders.
Materials and Methods: A literature review was conducted using databases including PubMed, Scopus, and Google Scholar. Clinical trials, meta-analyses, and reviews published in English between 2006 and 2025 were included. Studies addressing therapeutic outcomes, neurobiological mechanisms, and safety considerations of psychedelic-assisted therapies were analysed.
Results: In publications included in this literature review, psilocybin demonstrated robust antidepressant effects, benefits in substance use disorders, and reductions in anxiety following limited dosing sessions. MDMA-assisted psychotherapy showed strong efficacy in PTSD, with high remission rates. LSD exhibited promising effects in anxiety and substance use disorders. Ketamine produced rapid antidepressant and anti-suicidal effects in depression and showed potential in addiction and anxiety, although results in PTSD were mixed.
Conclusions: Psychedelic-assisted therapies represent a promising and scientifically credible expansion of psychiatric treatment options. While associated risks necessitate careful screening and clinical oversight, evidence supports their role as adjunctive or alternative interventions for selected patients, warranting further large-scale and long-term investigation.

Keywords: psychedelics, psychedelic therapy, hallucinogens, depression, substance use disorders, PTSD, anxiety, psilocybin, MDMA, LSD, ketamine

1. Introduction

1.1 History of psychedelics

Psychedelic substances have long been appreciated for their entheogenic and hallucinogenic effects. They have been widely used in religious, medical, and recreational settings for thousands of years. Strains of mushrooms containing psilocybin are present across most of the world's climates, and regionally unique species exist in isolated parts of land such as New Zealand and Australia [1]. Earliest evidence suggesting the usage of psychedelics dates back to the Neolithic period, with psychoactive mushrooms appearing in cave paintings as early as 8500 BCE [2]. Psychedelic substances may have influenced culture and religion in profound ways. Indigenous cultures in South and Mesoamerica incorporated mushrooms containing psilocybin, cacti containing mescaline, and ayahuasca into ceremonial healing rituals [3]. Danny Nemu [4] suggests that groundbreaking religious visions of Old Testament Prophets might have been caused by the ingestion of psychedelic substances. Usage of Amanita muscaria might have played a significant role in the religious rituals of Dionysus and Apollo [1]. Chemical synthesis of mescaline by Heffter in 1896 and LSD by Hoffman in 1938 brought psychedelics to the forefront of scientific discourse and paved the way to a wave of studies in the 1960s and 1970s, which researched their possible medical applications, including treatment for depression, substance dependence disorder, and anxiety. Criminalization and social stigma, emerging as an effect of the war on drugs, made further experiments on the medical usage of psychedelics difficult [5]. In recent years, however, with advances in neuroscience [2], we have seen a renewed interest in these substances that allowed for a loosening of restrictions on experimentation and research in the field of possible application of psychedelics in medical settings, especially in psychiatry and psychotherapy.

1.2 Neurobiological mechanisms

Psychedelics are a heterogeneous group of substances, usually divided into classic psychedelics (LSD, psilocybin, DMT) and atypical psychedelics (ketamine, MDMA) [6]. Classic psychedelics usually work as 5-HT2A receptor agonists and atypical compounds, although they produce similar psychological effects, have different working mechanisms, such as NMDA receptor antagonism in the case of ketamine. A crucial contribution in recent literature was the discovery of the ability of psychedelics to stimulate neuroplasticity [6]. Psychedelics have been shown to stimulate synaptogenesis, dendritic spine growth, and induce long-term changes in brain activity by modulating the work of signaling pathways involving BDNF (brain-derived neurotropic factor), TrkB, mTOR, and MAPK cascades [7]. Psychedelics have also been shown to increase expression of genes (Arc, c-Fos, Egr-1) in the prefrontal cortex, amygdala, claustrum, thalamus, and hippocampus. Stimulated expression of c-Fos was correlated with increased concentration of NMDA and 5-HTA2 receptors. Research suggests that the enduring effects of psychedelics may be in part caused by long-lasting changes in the epigenome in neurons [8]. A 7-day-long intake of LSD was shown to greatly modify genes connected with the development of neurons, their growth, death, and possible survival [8].

1.3 Aim of this article

Advances in psychiatry and neuroscience have shed new light on our understanding of illnesses such as depression, post-traumatic stress disorder, and substance abuse disorder. Taking into consideration limitations of conventional treatment, such as medication side effects that lead to 23% of patients taking serotonin reuptake inhibitors dropping out of treatment [9], as well as delayed therapeutic effect and partial response, has prompted the medical community to consider alternatives to standard medications. In this changing landscape, psychedelics reemerged as substances with possible therapeutic properties. Their ability to induce neuroplastic activity, as well as to facilitate long-lasting psychologically beneficial changes in behavior, compels clinical interest. Importantly, this article does not suggest that psychedelics could or should replace established psychiatric medications; rather, these substances need to be viewed as potential complementary forms of therapy or as a possible solution in cases of treatment resistance. This literature review aims to analyze evidence from different scientific domains, including neurobiology, psychiatry, and neuropharmacology, to assess the potential role of psychedelics in the future of psychiatric practice.

2. Methodology:

A systematic literature review was conducted. Multiple academic databases were searched, including Google Scholar, PubMed, and Scopus. The inclusion criteria were keyword matching, research-oriented nature of the article, date, and language of publication. Because of a huge number of articles, the selection had a cascading character and was carried out on the basis of keywords applied. In the first phase, the following keywords: “psychedelic”, “psychedelic treatment”, “psychedelic therapy” were used. In the second phase, the corpus was narrowed through a selection based on the keywords: “psilocybin therapy”, “LSD therapy”, “MDMA therapy”, “ketamine therapy” Finally a smaller number of texts was chosen by using additional keywords “psilocybin treatment resistant depression therapy”, “psilocybin substance use disorder therapy”, “psilocybin PTSD therapy”, ”psilocybin anxiety therapy”, “LSD treatment resistant depression therapy”, “LSD substance use disorder therapy”, “LSD PTSD therapy”, ”LSD anxiety therapy”, “MDMA treatment resistant depression therapy”, “MDMA substance use disorder therapy”, “MDMA PTSD therapy”, ”MDMA anxiety therapy”, “ketamine treatment resistant depression therapy”, “ketamine substance use disorder therapy”, “ketamine PTSD therapy”,” ketamine anxiety therapy”. Medical and neuroscience-focused articles published between 2006 and 2025 were selected for further study. Only research-based articles written in English were included in this review. The chosen articles comprised peer-reviewed research articles, meta-analyses, and systematic reviews written about the therapeutic use, neurobiological mechanisms, safety, and clinical outcomes of psychedelic usage in psychiatric conditions. In total, 49 studies met all the inclusion criteria and were included in this literature review.

3. Results

3.1 Psilocybin

Psilocybin, as for now, shows the greatest promise in its antidepressant properties. In a randomized, double blind clinical trial, Carhart Harris [10] compared psilocybin therapy with escitalopram in 59 patients suffering from major depressive disorder. After 6 weeks of study, psilocybin turned out to be equally successful in primary outcomes as escitalopram. However, long-term remission occurred in 57% of patients in the psilocybin group and 28% in the escitalopram group. Other secondary outcomes, such as emotional responsiveness and

psychological well-being, favored psilocybin. It is also important to mention that psilocybin achieved these effects after only 2 dosing sessions, where escitalopram was administered daily, which highlights one of the most fundamental differences in therapeutic programs [11].

When it comes to substance abuse disorders, evidence is also compelling. In a pilot study from 2015 [12], 10 patients suffering from alcohol dependency syndrome were administered psilocybin in one or two sessions. Volunteers, in addition to psilocybin, also attended therapy sessions and received Motivational Enhancement Therapy. The author reports that in the weeks following the administration of the drug, the number of heavy drinking days decreased on average by 26 percentage points and a 27% decrease in total alcohol consumption. Psilocybin also reduced cravings for alcohol by 50%. Reduced levels of cravings were maintained for over 36 weeks. Although this study did not compare psilocybin with other pharmacotherapies, such as naltrexone, outcomes were comparable or superior to those usually observed in standard treatments. These results were recently recreated in a double blind randomized clinical trial from 2022 [13] that compared the effectiveness of psilocybin with that of diphenhydramine. In the psilocybin administered group, the number of heavy drinking days during the 32-week double blind period was 9,7% while in the diphenhydramine-administered group, heavy drinking days constituted 23,6% of days during the study. Neurobiological research suggests that psilocybin may change pathological reward-seeking behavioural mechanisms while enhancing motivation to positive changes, introspection, and psychological flexibility-mechanisms not directly targeted by conventional addiction medications [14].

Research on psilocybin administration in post-traumatic stress disorder therapy remains preliminary, but it is still developing. A study protocol published by Davis [15] suggests a proof-of-concept study examining psilocybin-assisted therapy for war veterans suffering from post-traumatic stress disorder. The researchers recruited 15 military veterans with treatment-resistant PTSD and administered them psilocybin with preparatory and post-administration therapy sessions. While MDMA supported therapy in severe PTSD cases demonstrates, at the moment, the strongest empirical support, psilocybin is hypothesised to achieve positive therapy outcomes through promoting neural plasticity and decreasing amygdala reactivity during emotion processing, thus exerting antidepressant and anxiolytic properties, increasing patients' ability to process traumatic experiences [16].

Psilocybin has also demonstrated clinically significant positive effects in cases of patients experiencing severe anxiety associated with life-threatening illness [17]. A randomised, double-blind, placebo-controlled study from 2016 showed that psilocybin-assisted psychotherapy was able to rapidly reduce anxiety and depression symptoms in cases of cancer patients. Notably, improvements in anxiety and depression were accompanied by improved quality of life, reduced existential distress, increased acceptance of mortality, and greater overall psychological well-being. Described changes were sustained at the 6-month follow-up in about 80% of patients. Interestingly, beneficial effects were strongly correlated with the intensity of subjective meaning-oriented or mystical-type experiences during the psilocybin session [17].

3.2 LSD

Early LSD studies suggested that LSD- assisted therapy could produce long-lasting reduction in symptoms of depression after limited administration. Review of studies following the discovery of LSD concluded that after a one-time application, depression symptoms were reduced in 79% of participants [18], but it must be noted that studies from the 1960s often had methodological shortcomings. Recent research suggests that LSD may exert antidepressant effects by reducing activity of the amygdala and superior temporal gyrus, which shows

hyperactivity in the brains of people suffering from depression [19]. A recent randomized, double-blind, placebo-controlled phase 2 study [20] found that after 2 sessions of LSD treatment, ratings on the Hamilton Depression Rating scale decreased with a mean difference of -7. The results of the Beck Depression Inventory were consistent with HDR, showing a mean difference of -6,1 points.

Meta-analysis from 2012 of randomised controlled trials with a total of 536 participants suffering from alcohol use disorder [21] found that a single dose of LSD (3 μg/kg) with accompanying therapy sessions brought significant beneficial effects on alcohol misuse in short (2-3 months) and medium term (6 months post-treatment). 3 out of 6 analysed trials reported maintained abstinence from alcohol in short-term follow-up. Suggested mechanisms for LSD's beneficial effects in the therapy of substance abuse disorder include: enhancing patients' insight into their maladaptive behaviours, disruption of unhealthy stress-relieving mechanisms, and increasing their motivation for positive change [14]. It is important to mention that modern interpretations emphasise that therapeutic benefit arises from interaction between psychedelic experience and structured psychotherapy rather than from pharmacological effects alone.

There have not been enough studies conducted yet to be able to safely state whether LSD is effective in PTSD therapy. Nonetheless, LSD is recognised as a potential addition to trauma-focused therapy. Reviews on LSD-assisted PTSD therapy [16] note that the substance may reduce experimental avoidance, increase acceptance and connectedness, and allow for emotional engagement with traumatic material, thus being able to work through trauma with the help of a qualified psychotherapist.

Strongest contemporary evidence for LSD- assisted therapy comes from a recent open-label prospective study with 12-month follow-up [22]. Research demonstrated a reduction in anxiety symptoms after LSD-assisted therapy. Decrease in anxiety symptoms was measured in the State-Trait Anxiety Inventory. It is worth mentioning that other favourable personality changes also occurred after LSD-assisted therapy, such as reduced neuroticism and increased extraversion [20]. Participants reported long-term improvements in quality of life and no serious adverse effects in the follow-up period.

3.3 MDMA

Although MDMA has not yet been evaluated in large medical trials for major depressive disorder, evidence points to substantial and clinically relevant antidepressant effects, especially in depression related to trauma [23]. In Phase 3 PTSD trial, depressive symptoms measured by the Beck Depression Inventory, in the MDMA assisted therapy group were reduced compared with the placebo group (mean Δ for MDMA group=-19,7, while mean placebo Δ=-10,8). Notably, reductions were sustained. Antidepressant effects of MDMA might be caused less by direct elevation of neurotransmitter levels and more by enhanced emotional engagement, greater self compassion, and improvement in interpersonal functioning. It has also been suggested that MDMA's empathogenic properties can strengthen the relationship between therapist and patient, which may be an additional benefit of incorporating it into the therapy process.

There are not many studies conducted on MDMA assisted therapy in substance use disorders, but a few examples remain promising. In 2021, a pilot study [24] was conducted in which 14 patients with alcohol usage disorder after a detoxification period received psychotherapy alongside 2 sessions with MDMA. At 9 months post detox, the average consumption of alcohol by participants dropped from 130.6 units per week (amount consumed before therapy) to just

18.7 units. This study, although preliminary, provides evidence for good tolerance and lack of meaningful side effects of MDMA therapy while supporting the recovery process of patients, as we can see in the reduced number of units of alcohol consumed. High rates of comorbid alcohol and substance use disorders were present in MDMA assisted PTSD trials, yet treatment effects did not diminish in these populations [23]. There is a possibility that MDMA therapy may target underlying mechanisms of both PTSD and substance use disorders, such as trauma-related avoidance.

MDMA-assisted psychotherapy currently has its strongest empirical support in the treatment of PTSD. Randomised, double blind, placebo-controlled trials [25] demonstrate statistically and clinically meaningful reductions in symptoms of PTSD after administration of MDMA enhanced therapy. In the phase 3 trial from 2021 [23], MDMA therapy resulted in greater reductions in Clinician-Administered PTSD Scale for DSM-5 compared with the placebo group. At the endpoint of the study, 67% of participants in the MDMA group no longer met diagnostic criteria for PTSD, compared with 32% in the placebo group. It is worth mentioning that remission rates were much higher, at 33% in the MDMA group, contrasting with only 5% remission rate in the placebo group. Models suggest that MDMA inhibits the sensation of fear and stimulates memory reconsolidation by reducing amygdala and insular hyperreactivity and increasing connectivity between the limbic region and the prefrontal cortex. Feduccia [26] proposes that MDMA's combined effects on serotonin, norepinephrine, dopamine, and oxytocin allow to overwrite traumatic memories when revisited in a state of emotional safety and empathy induced by MDMA.

MDMA has also found some success in social anxiety treatment. A randomised, double blind, placebo-controlled pilot study was conducted between 2014 and 2017 on 12 autistic participants with social anxiety disorder [27]. Changes in the severity of social anxiety disorder were measured using the Liebowitz Social Anxiety Scale (LSAS). Reduction in social anxiety disorder symptoms was meaningfully greater in the MDMA group than in the placebo group (75% of participants from the MDMA group experienced reduced symptoms versus just 50% in the placebo group). Reductions in the severity of symptoms were retained in the 6-month follow-up. Limitations of the study must be acknowledged - sample size was small, and the fact that all of the participants received autism spectrum diagnosis limits potential applicability to the general public. Nonetheless, findings emphasise the need for future research.

3.4 Ketamine

Ketamine has demonstrated the strongest potential in the treatment of major depressive disorder, especially treatment-resistant depression. In randomised, controlled trials [28], subanesthetic doses of intravenous racemic ketamine produce rapid antidepressant effects and substantial reduction in suicidal thoughts. Effects peak around 24 hours, and symptom relief tends to last 7-14 days after infusion. No decrease in therapeutic effectiveness was observed, which suggests that chronic administration could be useful in maintaining therapeutic effects. In meta-analysis mean response and remission rate of major depressive disorder were 55,3% (response) and 28,9% (remission) [29]. It is worth mentioning that in other studies response rate was as high as 68,8% [30]. Meta-analysis from 2018 [31] found that depression symptoms measured in the Montgomery-Åsberg Depression Rating Scale were reduced by more than 50% after a single dose of ketamine. This effect lasted 7 days. Ketamine's antidepressant effects are mainly mediated by increasing presynaptic glutamate release, which is caused by blocking presynaptic NMDA receptors on inhibitory neurons in the prefrontal cortex and by blocking postsynaptic NMDA receptors in the hippocampus. Activated glutamate receptors subsequently facilitate the release of dopamine and serotonin, thus causing ketamine's antidepressant effects [32]. This

mechanism of action varies considerably from standard depression medications and even other psychedelic-based therapies, which can prove to be especially effective when confronted with therapy-resistant depression.

Despite its own misuse potential, ketamine has demonstrated substantial anti-addictive properties in controlled contexts. In a randomized clinical trial [33], 48,2% of cocaine dependent individuals were able to maintain 2-week abstinence in contrast to just 10,7% in the control group. Volunteers from the ketamine group were also 53% less likely to relapse compared to the control group. Similarly, ketamine infusions combined with motivational enhancement therapy and with mindfulness-based behavioral treatment reduced cannabis use without adverse events and remained reduced at the end of the 6-week study [34]. Properties of ketamine to mitigate substance use disorders may involve the disruption of memory formation and the modulation of neurotrophic signaling. Ketamine, by its ability to increase BDNF expression, may impair the reconsolidation of drug-related memories, thereby decreasing cravings and reducing the reinforcing effects of morphine [25].

The evidence for ketamine therapy for PTSD has been mixed. Some randomized and observational studies have demonstrated rapid reductions in PTSD symptom severity following ketamine infusions, especially in patients with comorbid depression [28]. However, in some recent meta-analyses, ketamine failed to demonstrate a statistically significant advantage over placebo, and in some cases, it even accelerated symptoms of PTSD [35]. Other meta-analyses [36] stated that ketamine demonstrated a significant decrease in PTSD symptoms both 24 hours after infusion and after the end of the study. These contradictory results highlight the need for more large-scale studies to be conducted before determining the safety and efficacy of ketamine infusions in PTSD therapy.

Ketamine has also shown promising results across anxiety-related disorders [28]. Repeated intramuscular administration of ketamine to patients diagnosed with generalised anxiety disorder reduced anxiety scores by 50% from baseline. Reductions were maintained for 7 months after treatment. In a randomized, placebo-controlled study of ketamine therapy for social anxiety disorder [37], ketamine infusions reduced LSAS results by a mean of 22,67±7,28 at day 2 and by more than 35% for 6 out of 18 participants.

4. Risks and Concerns

Psilocybin is generally regarded as having a favorable physiological safety profile, with low toxicity and minimal risk of dependence. However, psychological risks are important to consider, especially in vulnerable populations. Acute adverse reactions may include: anxiety, fear, confusion, nausea, dysphoria [38], especially in inadequately controlled settings or in cases of patients with a history of anxiety spectrum disorders. Nevertheless, in long-term follow-up up patients with anxiety spectrum disorders tend to experience improved quality of life and reduced frequency of panic attacks after administration of psilocybin [17], which suggests that although such patients may require additional attention and support during therapy sessions, results of such treatment can prove especially beneficial for them. Transient increases in blood pressure and heart rate have also been reported [12], which necessitate additional screening for cardiovascular disorders in patients qualified for clinical trials. A major concern is the potential for psilocybin to accelerate the development of latent schizophrenia-spectrum disorders. Psilocybin's agonism of 5-HT2A receptor stimulates similar neural pathways to those implicated in psychosis, and psilocybin-induced states can resemble positive symptoms of schizophrenia, such as visual and auditory hallucinations, paranoia, and delusions [39].

LSD shares many of psilocybin's risks but presents additional challenges due to its long duration of action, lasting up to 12 hours [40]. However, prolonged changes in patients' state of consciousness do not increase the likelihood of adverse psychological effects such as fear and paranoia [41]. LSD's capacity to induce a psychosis-like state raises concerns for individuals predisposed to psychotic disorders. Hallucinogen persisting perception disorder (HPPD), although rare, has been reported following LSD use [42]. The condition consists of partial recurrence of perceptual disturbances that appeared during previous hallucinogenic "trips" without recent use of a hallucinogenic substance. Triggers causing HPPD episodes in studies analysed are physical or mental stress, alcohol intake, cannabis consumption, and sexual intercourse. The majority of HPPD cases in the analysed literature have been induced by LSD or PCP. HPPD remains a major cause for concern when considering large scale implementation of LSD-based therapy, and thus it underlines the need for more extensive research, especially studies focused on potential causes, treatments, and frequency of this condition.

MDMA varies considerably from classic psychedelics and presents a distinct risk profile. Acute adverse effects include hyperthermia, dehydration, hyponatremia, tachycardia, and hypertension, especially in uncontrolled environments [43]. In contrast to psilocybin and LSD, MDMA intake can lead to significant life-threatening complications such as serotonin syndrome, rhabdomyolysis, disseminated intravascular coagulation, aortic dissection, intracranial hemorrhages, severe hepatotoxicity, and even liver failure [44]. Many studies demonstrated the occurrence of cognitive dysfunction after MDMA intake [45]. However, in many of these studies volunteers have taken the substance more than once, and long term studies of patients receiving MDMA therapy did not demonstrate similar intellectual impairments [43]. Another difficulty of MDMA-therapy is the substance's potential for misuse and addiction, especially when used in high doses [45]. To mitigate those risks, comprehensive safety protocols are recommended [43], such as monitoring MDMA's metabolite levels in urine in order to detect and eliminate possible misuse. A factor further reducing the possibility of misuse and addiction is the difference in emotional states between recreational users and patients undergoing therapy. First group associates MDMA intake with euphoric feelings, and the second, with recalling difficult memories and experiences [43].

Ketamine presents a distinct and multifaceted risk profile among substances considered for psychedelic-assisted therapy [31]. Main concern is ketamine's abuse and dependence potential, which must be acknowledged and adequately addressed in clinical studies and practice. While abuse potential is a major concern factor, it is not the only one. Growing evidence [46] highlights important concerns related to ketamine's neurotoxic effects under conditions of chronic or high dose exposure. Prolonged administration can disrupt normal glutamatergic signaling through sustained NMDA receptor antagonism, initiating a cascade of processes that may culminate in neuronal injury and apoptosis, especially in the hippocampus. Chronic ketamine usage has also been shown to activate neuroinflammatory pathways, including glial cell activation and release of pro-inflammatory cytokines, as well as to elevate levels of reactive oxygen species. These processes combined create a hostile neuronal microenvironment, increasing the risk of hippocampal cell death. Other risks of ketamine use must also be acknowledged. Common acute adverse side effects include: dissociation, dizziness, nausea, hallucinations, anxiety, and agitation. Ketamine also produces sympathomimetic cardiovascular effects, including transient increases in blood pressure and heart rate [47]. The most important side effect of chronic ketamine use on the urinary tract is ketamine-induced cystitis. Regular ketamine users are 3-4 times more likely to develop cystitis than the general public [48]. However infrequent, low-dose therapeutic regimens appear to carry minimal risks of the most serious complications. Symptoms that frequently appear even with moderate doses in a safe clinical environment are mild to moderate: dissociation, dizziness, and nausea [49].

Conclusions

The body of evidence reviewed demonstrates that psychedelic-assisted therapies represent a rapidly evolving and scientifically credible area of psychiatric research. Across multiple substances (psilocybin, LSD, MDMA, and ketamine), converging findings suggest that, when administered in carefully controlled clinical settings and combined with structured psychotherapy, psychedelics can produce meaningful and, in some cases, durable improvements in a range of psychiatric conditions that are often resistant to conventional treatments. These include major depressive disorder, substance use disorders, post-traumatic stress disorder, and anxiety-related conditions.

A central theme emerging from the literature is that the therapeutic potential of psychedelics cannot be reduced to their acute psychoactive effects alone. Rather, their clinical value appears to arise from a combination of neurobiological and psychological mechanisms. At the neurobiological level, psychedelics promote neuroplasticity through modulation of key signaling pathways involving glutamate, serotonin, BDNF, and downstream molecular cascades. These changes may facilitate synaptic remodeling and long-term alterations in neural networks implicated in mood regulation, fear processing, and reward learning. At the psychological level, psychedelics often induce experiences characterized by heightened emotional openness, increased insight, reduced avoidance, and enhanced cognitive and emotional flexibility. When embedded within a psychotherapeutic framework, these states may allow patients to engage with maladaptive beliefs, traumatic memories, or addictive behaviors in ways that are difficult to achieve through standard pharmacotherapy alone.

Among the substances reviewed, psilocybin and MDMA currently possess the most robust evidence base for specific indications. Psilocybin shows particular promise in depression, end-of-life anxiety, and substance use disorders, with several trials demonstrating effects that are comparable or superior to standard treatments despite minimal dosing. MDMA-assisted psychotherapy, in turn, has produced striking outcomes in PTSD, including high remission rates and sustained symptom reduction, suggesting that it may target core mechanisms of trauma pathology more directly than existing interventions. LSD, while supported by a smaller modern evidence base, has shown encouraging results in anxiety and substance use disorders and warrants further rigorous investigation. Ketamine, distinct in both mechanism and clinical profile, has already entered clinical practice for treatment-resistant depression and shows additional promise in addiction and anxiety, although findings in PTSD remain inconsistent.

At the same time, this review underscores that psychedelic therapies are not without risks. Acute psychological distress, cardiovascular effects, neurocognitive concerns, and, in certain populations, the potential exacerbation of psychosis-related vulnerabilities must be carefully considered. Ketamine, in particular, presents challenges related to abuse potential, neurotoxicity at high or repeated doses, and urological complications. MDMA carries unique physiological risks, while classic psychedelics raise concerns regarding prolonged altered states of consciousness and rare but serious perceptual disturbances. These risks highlight the necessity of strict screening, dosing control, therapeutic supervision, and long-term follow-up in both research and clinical settings.

Importantly, the evidence reviewed does not support the notion that psychedelics should replace established psychiatric treatments. Rather, their most appropriate role appears to be as adjunctive or alternative interventions for carefully selected patients, particularly those who have not benefited from standard approaches. The success of psychedelic-assisted therapy is

closely tied to the quality of preparation, therapeutic support, and integration, emphasizing that these substances function best as catalysts within a broader therapeutic process rather than as stand-alone pharmacological solutions.

In conclusion, psychedelics occupy a unique position at the intersection of neuroscience, psychology, and psychiatry. While substantial challenges remain, the accumulating evidence suggests that psychedelic-assisted therapies may meaningfully expand the therapeutic landscape of psychiatry. Continued interdisciplinary research and cautious clinical implementation will be essential to ensure that their potential benefits are realized while minimizing risks to patients.

Supplementary materials

Not applicable.

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Adam Wolski - conceptualization, methodology, formal analysis, writing - review and editing, formal analysis, supervision

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Declaration of Generative AI and AI-Assisted Technologies

In preparing this work, the authors used ChatGPT (OpenAI) for the purpose of improving language and readability, text formatting, and grammar correction. After using this tool/service, the authors have reviewed and edited the content as needed and take full responsibility for the content of the publication.

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