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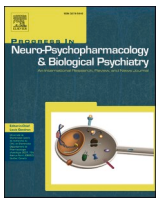

An overview of psilocybin, LSD, MDMA, and ketamine in revitalizing psychedelic-assisted therapy: Insights, limitations and future directions

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ABSTRACT

The resurgence of psychedelic-assisted psychotherapy marks a pivotal evolution in mental health treatment, challenging traditional paradigms by integrating compounds such as psilocybin, LSD, MDMA, and ketamine into clinical practice. Historically marginalized due to regulatory and societal concerns, these agents are now gaining recognition for their unique neurobiological mechanisms and therapeutic potential in addressing complex conditions like depression, PTSD, and addiction. Unlike conventional treatments, psychedelics exert their effects primarily through modulation of serotonin receptors and brain network connectivity, with each substance demonstrating distinct pharmacological profiles and clinical applications. Notably, psilocybin and LSD share serotonergic pathways but differ in receptor specificity and subjective effects, while MDMA's empathogenic properties and ketamine's rapid antidepressant action offer alternative therapeutic avenues. Recent FDA breakthrough therapy designations for psilocybin and MDMA underscore a shift toward evidence-based acceptance, yet the field remains challenged by methodological limitations, regulatory barriers, and ethical considerations. This narrative review synthesizes historical developments, mechanistic insights, and clinical outcomes, emphasizing the need for rigorous research, diverse patient cohorts, and thoughtful integration of psychedelics with psychotherapeutic modalities to realize their full therapeutic promise.

1. Introduction

The landscape of mental health care is undergoing a profound transformation as psychedelic-assisted psychotherapy emerges from decades of regulatory restriction into the forefront of clinical innovation (Argento et al., 2021). This renewed interest is not merely a revival of past practices but represents a convergence of historical wisdom, modern neuroscience, and evolving therapeutic needs (Vollenweider and Preller, 2020; Aday et al., 2019). Psilocybin, LSD, MDMA, and ketamine—each with distinct legal, cultural, and pharmacological identities—are now being systematically evaluated for their capacity to address treatment-resistant depression, substance use disorders, PTSD, and existential distress (De Gregorio et al., 2021a; Gill et al., 2020). While this review focuses on psilocybin, LSD, MDMA, and ketamine, other psychedelic compounds such as mescaline, DMT, ayahuasca, and ibogaine are also being studied for their therapeutic potential in a variety of mental health conditions (see Table 1 for an overview of additional compounds and ongoing clinical trials).

Unlike traditional pharmacotherapies, which often target single neurotransmitter systems and require prolonged administration, psychedelics induce rapid and sometimes enduring changes in mood, cognition, and behavior through complex interactions with serotonin receptors and brain network dynamics (De Gregorio et al., 2021a; Gill et al., 2020). For example, the activation of 5-HT2A receptors by psilocybin and LSD leads to increased cortical entropy and connectivity, potentially facilitating psychological flexibility and emotional

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processing (Carhart-Harris, 2019a). In contrast, MDMA's primary action as a monoamine releaser and oxytocin enhancer uniquely positions it for trauma-focused therapy, while ketamine's NMDA antagonism offers rapid relief for depressive symptoms, albeit with distinct safety and abuse considerations (Wolfgang et al., 2025).

The therapeutic renaissance of these compounds is rooted in both ancient ritualistic use and mid-20th-century clinical experimentation, yet it is only in recent years—fueled by rigorous clinical trials and shifting regulatory stances—that their medical potential is being systematically realized (Aday et al., 2019; Nielson and Guss, 2018). FDA breakthrough therapy designations for psilocybin and MDMA highlight not only their efficacy but also the urgent need for novel interventions in mental health (Canady, 2024; Sinha, 2024). However, significant challenges persist, including legal restrictions, public stigma, and the necessity for robust, diverse research methodologies (Ledwos et al., 2022a; Rosenblat et al., 2024).

This review critically examines the intertwined historical, mechanistic, and clinical dimensions of psychedelic-assisted psychotherapy. By comparing and contrasting the pharmacological actions and therapeutic outcomes of psilocybin, LSD, MDMA, and ketamine, we aim to elucidate both the shared and unique contributions of each agent. Ultimately, a nuanced understanding of these therapies will inform their responsible integration into modern psychiatric practice and guide future research directions.

2. Methodology

This manuscript employs a narrative review methodology to synthesize existing literature on psychedelic-assisted therapies. The review covers research from early 20th-century studies through to the current resurgence of clinical interest.

A literature survey was conducted across PubMed, Scopus, and Web of Science using keywords such as "psychedelic-assisted psychotherapy," "psilocybin," "LSD," "MDMA," "ketamine," "PTSD," and "depression." The search focused on peer-reviewed articles published from 1960 onwards.

Studies were selected based on their relevance to the therapeutic use of psychedelics, including empirical data, critical analyses, historical context, regulatory considerations, ethical issues, and clinical outcomes. This narrative review does not follow formal systematic review protocols and therefore does not include a PRISMA flow diagram or structured inclusion/exclusion table.

Data extraction emphasized key themes such as biochemical effects of psychedelics, pharmacological mechanisms, clinical efficacy, safety, and regulatory challenges.

2.1. Ethical considerations

Since this research is a literature review, it did not involve direct interaction with human subjects or animals, thus negating the requirement for ethical approval. However, the manuscript underscores the ethical considerations pertinent to the use of psychedelics in research and clinical settings, particularly regarding informed consent, risk management, and the safety of participants.

2.2. Limitations

As this is a narrative review, no PRISMA flow diagram or structured inclusion/exclusion tables are provided. The selection of studies was based on relevance and contribution to the topic rather than a formal systematic protocol.

2.3. From promise to restriction: the historical and contemporary landscape of psychedelic research in mental health treatment

The scientific exploration of psychedelics predates the synthesis of LSD in 1938 (Aday et al., 2019; Hofmann, 1979). Early investigations into mescaline, derived from the peyote cactus, and DMT, a naturally occurring tryptamine, were conducted in the late 19th and early 20th centuries, laying the groundwork for later research into the therapeutic properties of these substances (Gallimore and Luke, 2015; Barker, 2018). Albert Hofmann's creation of LSD at Sandoz Laboratories in 1938 marked a watershed moment, catalyzing a wave of clinical experimentation in the 1950s and 1960s (Gallimore and Luke, 2015; Hofmann, 1970). During this period, Harvard psychologists Timothy Leary and Richard Alpert (Ram Dass) initiated pioneering studies on psilocybin's potential to treat conditions such as addiction, depression, and PTSD, while more recently, Roland Griffiths has contributed to the modern resurgence of clinical research (Nielson and Guss, 2018; Sharma et al., 2023).

The trajectory of psychedelic research was dramatically altered by regulatory interventions and shifting public attitudes (Nielson and Guss, 2018; Dahlberg et al., 1968). The Controlled Substances Act of 1970, influenced by both societal fears and government agencies—including documented involvement by the US CIA in shaping public perception—effectively halted most clinical research for decades (Marks, 2018). This period of stagnation was characterized by heightened stigma and limited scientific progress (Silberner, 2022).

Recent years have witnessed a significant revival, fueled by advances in neuroscience, a growing body of clinical evidence, and evolving regulatory landscapes (Vollenweider and Kometer, 2010). The FDA's breakthrough therapy designations for psilocybin and MDMA underscore a paradigm shift, yet significant challenges remain, including persistent regulatory barriers, the need for rigorous long-term safety data (especially for compounds like ketamine), and the risk of media-driven overhype (Canady, 2024; Siegel et al., 2023).

2.4. Mechanisms of action: understanding psilocybin's role in serotonergic pathways and its therapeutic effects

Psilocybin, a classic serotonergic psychedelic, exerts its primary effects through agonism at the 5-HT2A receptor, particularly within the

Table 1
Selected psychedelics beyond the four main compounds: current clinical trials and therapeutic indications.

Compound	Chemical class	Traditional/indigenous use	Key mechanism	Current clinical indications	Reference
Mescaline	Phenethylamine	Peyote cactus rituals (Americas)	5-HT2A agonist	Depression, Alcohol Use Disorder	(Vamvakopoulou et al., 2023)
DMT	Tryptamine	Ayahuasca ceremonies (Amazon)	5-HT2A agonist, sigma-1 mod.	Major Depressive Disorder, Anxiety	(Egger et al., 2024)
Ayahuasca	Mixed (DMT + MAOI)	Amazonian shamanic healing	DMT + MAOI (harmala alkaloids)	Depression, PTSD, Addictions	(Rossi et al., 2022)
Ibogaine	Indole alkaloid	Bwiti rituals (Africa)	NMDA antagonism, kappa opioid	Opioid Use Disorder, Alcohol Use Disorder	(Mash, 2023)
Salvinorin A	Diterpene	Mazatec rituals (Mexico)	Kappa opioid receptor agonist	Depression, Addiction (early phase)	(Butelman and Kreek, 2015)
2C-B	Phenethylamine	Synthetic, recreational	5-HT2A/2C agonist	Anxiety, PTSD (exploratory)	(Gil-Martins et al., 2025)

prefrontal cortex (Carhart-Harris, 2019a). Recent studies have revealed that psychedelics bind not only to surface 5-HT2A receptors but also to internalized receptors associated with the Golgi apparatus, which may contribute to their neuroplastic and lasting therapeutic effects (Vargas et al., 2023). These neuroplastogenic properties, including the promotion of dendritic spine growth and synaptogenesis, are believed to underlie the sustained clinical benefits observed in mood and anxiety disorders (Sapienza, 2023; De Vos et al., 2021).This mechanism is shared with LSD, though psilocybin's shorter duration and lower potency may make it more manageable in clinical settings (Reis, 2024). Unlike MDMA, which primarily increases monoaminergic neurotransmission and oxytocin release, psilocybin's effects are more strongly linked to altered perception and cognition rather than pronounced emotional openness or empathy (Wolfgang et al., 2025).

Clinically, psilocybin has demonstrated significant efficacy in reducing depressive symptoms and existential distress, especially in patients with treatment-resistant depression and end-of-life anxiety (Borissova and Rucker, 2024). Compared to ketamine, which also produces rapid antidepressant effects via NMDA receptor antagonism and glutamate surge, psilocybin's benefits seem to be more enduring after only one or two sessions, while ketamine often requires repeated dosing for sustained effect. However, both agents appear to induce neuroplasticity, albeit through distinct molecular pathways (McCartney et al., 2022; Wang et al., 2023).

Importantly, psilocybin's safety profile is favorable, with low risk of dependence or withdrawal—contrasting with the abuse potential seen in ketamine (Wang et al., 2023). Adverse effects are generally limited to transient anxiety or confusion during the acute phase, and serious events are rare under supervised conditions (Sharma et al., 2023). Nevertheless, the evidence base for psilocybin is still limited by small sample sizes and short follow-up periods, and its efficacy relative to other psychedelics (such as LSD or MDMA) in head-to-head trials remains to be established (Ledwos et al., 2022a).

In summary, while psilocybin shares mechanistic and therapeutic overlap with other psychedelics, its unique profile—marked by a moderate duration of action, robust antidepressant effects, and favorable safety—positions it as a promising candidate for further clinical development. Future research should directly compare psilocybin with other agents like MDMA and ketamine to clarify optimal indications and patient selection.

2.5. Exploring the therapeutic potential of lysergic acid diethylamide (LSD): historical insights and clinical efficacy in psychological disorders

Lysergic acid diethylamide (LSD) has played a pivotal role in the evolution of psychedelic research since the 1950s, with a surge of clinical interest in the 1960s regarding its potential to address a spectrum of psychological disorders (Nichols, 2018; Liechti, 2017). Early and contemporary studies indicate that LSD may alleviate symptoms of depression, anxiety, addiction, and certain psychosomatic conditions. Notably, a large-scale clinical trial involving 567 participants demonstrated LSD's therapeutic effects across a wide dose range, supporting its potential utility in psychiatric care (Dos Santos et al., 2016).

2.6. Mechanistic distinctions and overlaps

LSD's pharmacological profile is both broad and unique among classical psychedelics (Vollenweider and Preller, 2020). Like psilocybin, LSD is a potent partial agonist at the serotonin 5-HT2A receptor, a mechanism central to the psychedelic experience and therapeutic effects (Carhart-Harris, 2019b). However, LSD distinguishes itself by engaging a wider array of serotonin receptor subtypes (including 5-HT1A and 5-HT2C), as well as dopaminergic and trace amine-associated receptors at higher doses (De Gregorio et al., 2021b). This pleiotropic receptor activity may underlie LSD's longer duration, more pronounced visual phenomena, and stimulating qualities compared to psilocybin, which is typically described as less intense and more introspective (Reis, 2024; Liechti, 2017).

Recent neuroimaging and connectivity studies reveal that LSD, like other psychedelics, disrupts the balance between brain network integration and segregation—markedly increasing global connectivity while reducing self-inhibition in occipital and subcortical regions (Ertl et al., 2025; Ruban and Kołodziej, 2018). These changes are thought to underpin the characteristic alterations in perception, cognition, and mood (Carhart-Harris, 2019b). Interestingly, both LSD and psilocybin enhance neuroplasticity and promote psychological flexibility, although LSD's effects may be more pronounced due to its longer half-life and broader receptor engagement (Calder and Hasler, 2023). In contrast, MDMA's mechanism is dominated by monoamine release and oxytocinergic activity, resulting in a distinct empathogenic profile, while ketamine's primary actions are mediated through NMDA receptor antagonism, leading to rapid but short-lived antidepressant effects (Wolfgang et al., 2025; *Neuroscientist*, 2024).

2.7. Clinical efficacy and psychological impact

Clinically, LSD has shown promise in reducing anxiety, depression, and addictive behaviors, with effects that can persist for weeks or months after a limited number of sessions (Fluyau et al., 2024). For example, recent placebo-controlled trials have demonstrated significant reductions in state and trait anxiety following LSD-assisted psychotherapy, with benefits maintained at follow-up. Compared to psilocybin, LSD's longer duration of action may allow for deeper exploration during therapeutic sessions but also necessitates more intensive monitoring and support (Reis, 2024).

LSD's psychological effects are notable for their intensity and breadth (Aday et al., 2019). Users frequently report profound alterations in cognition, self-perception, and emotional processing, including ego dissolution, heightened empathy, and a sense of interconnectedness. These experiences, while potentially transformative, can also be overwhelming or anxiety-provoking, underscoring the need for careful patient selection and skilled therapeutic support (Jacobs, 2023). In contrast, MDMA's effects are often described as more emotionally accessible and less perceptually disruptive, making it particularly suitable for trauma-focused therapy (Wolfgang et al., 2025).

2.8. Risks, ethical considerations, and clinical context

While LSD's safety profile is generally favorable in controlled settings, its long duration, potential for acute psychological distress, and rare but serious adverse events (e.g., persistent perceptual changes) require careful risk management (Breeksema et al., 2022; McNamee et al., 2023). Ethical considerations include the necessity for informed consent, thorough screening, and the provision of a supportive therapeutic environment. Compared to ketamine, which carries a higher risk of abuse and cognitive side effects, LSD's risks are primarily psychological rather than physiological (Liu et al., 2009).

2.9. Comparative summary and future directions

In summary, LSD shares core mechanistic features with other serotonergic psychedelics but stands out for its receptor diversity, prolonged effects, and pronounced alterations in consciousness (Vollenweider and Preller, 2020; De Gregorio et al., 2021b). Its efficacy in anxiety, depression, and addiction appears comparable to that of psilocybin, though direct comparative trials are lacking (De Gregorio et al., 2021b). The choice between LSD, psilocybin, MDMA, and ketamine in clinical practice should be guided by patient characteristics, therapeutic goals, and risk tolerance. Future research should prioritize head-to-head comparisons, standardized outcome measures, and long-term follow-up to clarify the relative advantages and limitations of each compound in psychedelic-assisted psychotherapy (Hogea et al., 2025; Ledwos et al.,

2022b).

2.10. MDMA-assisted therapy for PTSD: mechanistic distinctions, clinical outcomes, and comparative insights

MDMA (3,4-methylenedioxymethamphetamine) occupies a unique position among psychoactive compounds used in psychotherapy, particularly for post-traumatic stress disorder (PTSD) (Bird et al., 2021). Unlike classic psychedelics such as psilocybin and LSD, which primarily exert their effects through serotonergic receptor agonism, MDMA's mechanism centers on the robust release of monoamines—serotonin, dopamine, and norepinephrine—by reversing their respective transporters. This action is complemented by weak agonism at 5-HT1 and 5-HT2 receptors and a pronounced increase in oxytocin, a hormone associated with social bonding and trust (Wolfgang et al., 2025; De Gregorio et al., 2021b).

2.11. Mechanistic and clinical distinctions

MDMA's neurochemical profile underpins its distinctive clinical effects (Meyer, 2013). The surge in serotonin is chiefly responsible for MDMA's prosocial and empathogenic properties, including heightened empathy, openness, and emotional connectedness (Arnovitz et al., 2022). These features are particularly advantageous in trauma-focused psychotherapy, as MDMA can attenuate fear responses, reduce defensiveness, and facilitate the revisiting of traumatic memories in a supportive therapeutic context (Arnovitz et al., 2022). In contrast, classic psychedelics like psilocybin and LSD are more likely to induce perceptual and cognitive alterations, which, while sometimes beneficial for insight, may not directly foster the same degree of emotional trust or therapeutic alliance.

Recent neuroimaging and neuroendocrine studies suggest that MDMA's effects extend beyond monoamine release. By modulating amygdala activity and enhancing levels of brain-derived neurotrophic factor (BDNF), MDMA may promote fear extinction and memory reconsolidation—mechanisms thought to underlie its efficacy in PTSD (Pantoni et al., 2022; Feduccia et al., 2019). This is in contrast to ketamine, whose rapid antidepressant effects are mediated through NMDA receptor antagonism and glutamate surge, with less pronounced impact on social or emotional processing.

2.12. Clinical efficacy and comparative effectiveness

MDMA-assisted psychotherapy has demonstrated substantial and durable reductions in PTSD symptoms across multiple randomized controlled trials, leading to its FDA "Breakthrough Therapy" designation. Notably, the effect sizes observed in MDMA trials surpass those typically reported for standard pharmacotherapies such as SSRIs, which often require chronic administration and yield only modest benefits. In addition to symptom reduction, MDMA-assisted therapy has been associated with improved interpersonal relationships, emotional empathy, and community engagement—outcomes less frequently reported with other pharmacological interventions.

When compared to other psychedelic-assisted therapies, MDMA's unique ability to foster emotional safety and openness appears especially well-suited for patients with severe trauma or interpersonal distrust. While psilocybin and LSD may also promote psychological insight and emotional release, their effects are more variable and can include challenging perceptual experiences, which may not be ideal for all PTSD populations (Wolfgang et al., 2025).

2.13. Safety, risks, and ethical considerations

Despite its therapeutic promise, MDMA is not without risks. Acute adverse effects—such as insomnia, tachycardia, and transient increases in blood pressure—are generally mild and manageable within controlled clinical settings, particularly given the limited number of sessions required for therapeutic benefit (Fluyau et al., 2024). Concerns about neurotoxicity, abuse potential, and polydrug use remain relevant, especially outside of medical supervision; however, clinical trials to date have not identified significant long-term harms when MDMA is administered responsibly (Song et al., 2010).

MDMA's regulatory status as a Schedule I substance continues to pose barriers to research and implementation. Ethical considerations, including informed consent, patient screening, and careful monitoring, are paramount to ensure patient safety and public trust (Jacobs, 2023; Feduccia et al., 2023).

3. Conclusion and future directions

In summary, MDMA-assisted psychotherapy represents a novel and promising approach for individuals with treatment-resistant PTSD, offering rapid, robust, and enduring symptom relief that exceeds current standard treatments. Its unique pharmacological and psychological profile distinguishes it from classic psychedelics and ketamine, positioning MDMA as a valuable addition to the armamentarium for trauma-related disorders. Ongoing research should continue to clarify its long-term safety, optimal dosing protocols, and comparative effectiveness across diverse patient populations.

3.1. Ketamine: from anesthetic to rapid-acting antidepressant and pain modulator — mechanisms, clinical utility, and challenges

Ketamine, originally developed in 1962 as a safer alternative to phencyclidine for anesthesia, has evolved into a multifaceted therapeutic agent with applications extending beyond its dissociative anesthetic properties (Ivan Ezquerra-Romano et al., 2018). At anesthetic doses, ketamine induces analgesia, sedation, and amnesia while preserving respiratory and cardiovascular function, characteristics that have made it invaluable in surgical settings. More recently, subanesthetic doses of ketamine have garnered significant attention for their rapid and robust antidepressant effects, as well as for managing chronic pain syndromes resistant to conventional therapies (Goel et al., 2023).

3.2. Mechanisms underpinning therapeutic effects

Ketamine's primary mechanism involves non-competitive antagonism of the *N*-methyl-D-aspartate (NMDA) receptor, a subtype of glutamate receptor critical for synaptic plasticity and neuronal communication (Zanos and Gould, 2018). By selectively inhibiting extra-synaptic GluN2B-containing NMDA receptors, ketamine disrupts pathological glutamatergic signaling implicated in depression and pain. This blockade initiates a cascade of neurochemical events, including increased release of brain-derived neurotrophic factor (BDNF), activation of the mechanistic target of rapamycin (mTOR) pathway, and enhanced synaptogenesis (Fluyau et al., 2024; Zanos and Gould, 2018). These molecular changes facilitate rapid restoration of synaptic connectivity and plasticity, which are believed to underlie ketamine's swift antidepressant and analgesic effects.

Notably, ketamine's action is multifaceted: beyond NMDA receptor antagonism, its metabolites, such as (2*R*,6*R*)-hydroxynorketamine, may exert antidepressant effects via glutamate-independent mechanisms. Additionally, ketamine modulates α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors and inhibits hyperactivity in brain regions like the lateral habenula, which are implicated in depressive symptomatology (Zanos and Gould, 2018). This complex pharmacodynamics contrasts with classic serotonergic psychedelics (psilocybin, LSD) that primarily target 5-HT2A receptors, and with MDMA's monoaminergic and oxytocinergic effects, highlighting ketamine's unique therapeutic niche (Reis, 2024).

3.3. Clinical efficacy and limitations

Clinically, ketamine's rapid onset of antidepressant action—often within hours—represents a paradigm shift in treating treatment-resistant depression and acute suicidality. Single intravenous infusions yield response rates exceeding 60 % within 4 to 24 h, with effects lasting up to a week. However, the transient nature of these benefits necessitates repeated dosing or adjunctive therapies to sustain remission, raising questions about long-term safety and optimal maintenance protocols.

While ketamine's analgesic properties are well-established, especially in neuropathic and chronic pain syndromes, its psychiatric applications remain constrained by concerns over potential abuse, cognitive side effects, and urinary toxicity observed in recreational users (Ivan Ezquerra-Romano et al., 2018). These risks underscore the importance of stringent patient screening, monitoring, and regulatory oversight, particularly in populations with histories of substance use disorders.

3.4. Ethical considerations and research gaps

The promise of ketamine is tempered by ethical and practical challenges. The potential for dependency and misuse requires careful balancing of therapeutic benefits against risks, especially given the variability in regulatory frameworks worldwide (Ledwos et al., 2022c). Furthermore, the long-term neurocognitive effects of repeated ketamine exposure remain insufficiently characterized, necessitating robust longitudinal studies.

Current research is limited by small sample sizes, heterogeneous dosing regimens, and short follow-up durations, impeding definitive conclusions about ketamine's sustained efficacy and safety. Comparative studies evaluating ketamine alongside serotonergic psychedelics and MDMA are sparse but essential to delineate the most appropriate therapeutic contexts for each agent.

3.5. Ongoing controversies and limitations

Despite promising clinical outcomes, ketamine's long-term safety profile remains inadequately characterized. Reports of urinary and hepatic toxicity among recreational users raise concerns about potential adverse effects with repeated therapeutic dosing, particularly in patients with histories of substance use disorders. The risk of dependency and misuse necessitates rigorous patient screening and monitoring, yet standardized guidelines remain underdeveloped.

Regulatory bottlenecks further complicate ketamine's clinical integration. Although esketamine nasal spray has gained FDA approval, ketamine's off-label use as an antidepressant faces variable legal frameworks worldwide, impeding consistent access and research.

Placebo effects also pose interpretative challenges in ketamine trials, given the subjective nature of dissociative experiences that may unblind participants and influence outcomes. Moreover, media coverage has at times amplified ketamine's benefits, contributing to public overhype that may outpace the evidence base and obscure nuanced risk-benefit considerations (Azevedo et al., 2023).

3.6. Research gaps and future directions

Advancing ketamine's therapeutic integration demands larger, well-controlled trials encompassing diverse patient populations and standardized protocols. Investigations into novel formulations, enantiomer-specific effects, and synergistic combinations with psychotherapies may optimize efficacy while minimizing adverse outcomes. Additionally, elucidating ketamine's molecular mechanisms will inform the development of next-generation rapid-acting antidepressants with improved safety profiles.

3.7. Comparative mechanisms of action

All four compounds—psilocybin, LSD, MDMA, and ketamine—modulate neural circuits implicated in mood and cognition, but through distinct molecular pathways. Psilocybin and LSD primarily act as 5-HT2A receptor agonists, increasing cortical entropy and promoting neuroplasticity. MDMA's therapeutic effects are mediated by monoamine release and oxytocin elevation, facilitating emotional processing and fear extinction, especially in PTSD. Ketamine, in contrast, is a noncompetitive NMDA receptor antagonist that rapidly enhances synaptic plasticity through mTOR pathway activation. These mechanistic differences inform their respective clinical profiles and therapeutic indications. In Table 2 we directly compares and contrasts the mechanisms, efficacy, risks, and clinical utility of psilocybin, LSD, MDMA, and ketamine.

4. Conclusion

Ketamine exemplifies the expanding frontier of psychedelic-assisted therapies, bridging anesthetic utility with groundbreaking psychiatric and analgesic applications. Its rapid modulation of glutamatergic signaling and synaptic plasticity distinguishes it mechanistically and clinically from classic psychedelics and MDMA. However, realizing ketamine's full therapeutic potential requires addressing ethical concerns, refining treatment protocols, and conducting rigorous long-term studies. As mental health care evolves, ketamine stands as both a powerful tool and a catalyst for innovation in treating complex neuropsychiatric disorders.

CRediT authorship contribution statement

Kiana Askariyan: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition. **Mohammad Taghi Joghataei:** Validation, Conceptualization. **Samaneh Dehghan:** Writing – original draft, Visualization, Data curation. **Shabnam Nohesara:** Methodology, Investigation. **Leila Riahi pour:** Validation, Investigation. **Mohammad Hossein Mohammadi:** Methodology. **Nooshin Ahmadirad:** Writing – review & editing, Validation, Conceptualization.

Ethical statement

I confirm that I have reviewed and complied with the journal's Guide for authors and the Ethics in Publishing policy at www.elsevier.com/publishingethics.

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Table 2
Comparative analysis of mechanisms, efficacy, and clinical utility.

Compound	Main mechanism(s)	Key clinical indications	Relative efficacy	Key risks/ limitations
Psilocybin	5-HT2A agonist	Depression, end-of-life anxiety	High (depression, anxiety)	Short duration, legal status
LSD	5-HT2A agonist	Anxiety, cluster headache	Moderate (anxiety)	Long duration, legal status
MDMA	Monoamine releaser, 5-HT2A partial agonist	PTSD, social anxiety	High (PTSD)	Cardiovascular, neurotoxicity
Ketamine	NMDA antagonist	Depression, suicidality	Rapid, robust (depression)	Dissociation, abuse potential

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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