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IP Indian Journal of Neurosciences

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Short Communication

Ketamine, MDMA, and psychedelics: Emerging therapeutics in mental health

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Received: 22-02-2025; **Accepted:** 28-03-2025; **Available Online**: 14-04-2025

1. Introduction

Mental health disorders, including depression, PTSD, and anxiety, are leading causes of disability worldwide. Current treatments, such as antidepressants and psychotherapy, are not effective for all individuals, with many patients experiencing treatment resistance. Ketamine, MDMA (3,4-methylenedioxymethamphetamine), and classic psychedelics like psilocybin, LSD, and DMT (dimethyltryptamine) have emerged as potential breakthroughs, demonstrating rapid and sustained effects in otherwise refractory cases.

*1.1. Therapeutic evidence base and comparison (**Table 1**)*

1.1.1. Ketamine

Ketamine, a dissociative anaesthetic, acts as an N-methyl-D-aspartate (NMDA) receptor antagonist. It modulates glutamate signalling, promoting synaptic plasticity and neurogenesis.

1.1.1.1. Therapeutic applications

Depression: Intravenous ketamine has been shown to provide rapid relief from symptoms of major depressive disorder (MDD) and suicidal ideation. Berman et al. (2000)[1] demonstrated significant symptom reduction within hours of administration.

Chronic Pain and Anxiety: Low-dose ketamine infusions are being explored for these conditions.

1. Clinical evidence
    a. Esketamine (a ketamine enantiomer) was approved by the FDA in 2019 for treatment-resistant depression. It rapidly releases glutamate leading to brain-derived neurotrophic factor (BDNF) activation, reversing synaptic deficits in depression.
2. Challenges
    a. Potential for abuse due to dissociative and euphoric effects.
    b. Side effects include dissociation, hypertension, and nausea.

1.1.2. MDMA

3,4-Methylenedioxymethamphetamine, commonly called as ecstasy used as a tablet, and as molly if a crystal. It has stimulant and minor psychedelic properties. MDMA primarily increases serotonin release and inhibits serotonin reuptake, along with effects on dopamine and norepinephrine. Unique to MDMA is its prosocial and empathogenic properties, enhancing emotional processing and trust.

1. Therapeutic applications
    a. Post-Traumatic Stress Disorder (PTSD): MDMA-assisted psychotherapy has shown promising results for patients with severe PTSD. A Phase 3 trial led by MAPS (Multidisciplinary Association for Psychedelic Studies) demonstrated a 67% reduction in PTSD symptoms after MDMA-assisted therapy (Mitchell et al., 2021).[2]
    b. Social Anxiety: Particularly in autistic individuals, MDMA may reduce fear and enhance emotional connection.

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http://doi.org/10.18231/j.ijn.2025.013

2. Clinical Evidence
    a. MDMA has received a "Breakthrough Therapy" designation from the FDA for PTSD.
    b. Studies highlight the ability of MDMA to facilitate therapy by reducing fear responses and enabling emotional engagement.
3. Challenges
    a. Risks include potential neurotoxicity at high doses, cardiovascular effects, and risk of misuse.
    b. Public stigma and concerns about its recreational use complicate its therapeutic adoption.

1.1.3. Psychedelics

This group includes the following namely Psilocybin, LSD, DMT, and Ayahuasca. Classic psychedelics act primarily on the serotonin 5-HT2A receptor. They induce altered states of consciousness, promoting introspection and emotional breakthroughs.

1. Therapeutic Applications
    a. Depression and Anxiety: Psilocybin has shown rapid antidepressant effects, especially in treatment-resistant cases. Carhart-Harris et al. (2016)[3] demonstrated significant symptom reduction in patients with depression after psilocybin therapy.
    b. End-of-Life Distress: Patients with terminal illnesses have reported reduced anxiety and improved emotional well-being after psychedelic therapy.
    c. Addiction: Psychedelics, particularly psilocybin and ibogaine, are being investigated for their potential to treat substance use disorders.
2. Clinical Evidence
    a. Psilocybin is in Phase 3 clinical trials for MDD.
    b. Ayahuasca, a traditional Amazonian brew, is being explored for its effects on PTSD and addiction.
3. Challenges
    a. Mystical experiences, while therapeutic, can be overwhelming or distressing for some patients.
    b. Regulatory barriers and ethical concerns regarding altered states of consciousness remain significant hurdles.

Table 1: Comparison of ketamine, MDMA, and psychedelics[4]

Feature	Ketamine	MDMA	Psychedelics
Mechanism	NMDA receptor antagonist	Serotonin release and reuptake inhibitor	5-HT2A receptor agonist
Key Conditions Treated	Depression, suicidal ideation	PTSD, social anxiety	Depression, anxiety, addiction
FDA Approval Status	Approved (Esketamine for depression)	Breakthrough Therapy (PTSD)	Phase 3 trials (Psilocybin for MDD)
Time to Effect	Hours	Weeks (with therapy)	Weeks (with therapy)
Risk of Abuse	Moderate	Moderate	Low to moderate

2. Future Directions

1. Integration into Healthcare: Developing standardized protocols for administration and therapy integration.
2. Long-Term Safety Studies: Understanding neurotoxicity and psychological effects with prolonged use.
3. Public Awareness: Destigmatizing these substances through education and transparent communication of benefits and risks.

3. Conclusion

Ketamine, MDMA, and psychedelics represent a paradigm shift in mental health treatment. Their unique mechanisms of action and rapid therapeutic effects make them invaluable tools, particularly for treatment-resistant conditions. However, their integration into mainstream medicine requires addressing stigma, ethical concerns, and safety issues through continued research and policy reform.

4. Source of Funding

None.

5. Conflict of Interest

None.

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Cite this article Lingeswaran A. Ketamine, MDMA, and psychedelics: Emerging therapeutics in mental health. *IP Indian J Neurosci* 2025;11(1):.