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REVIEW ARTICLE

Ketamine Therapy in Psychiatry: A Comprehensive Review

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ABSTRACT

Ketamine, traditionally known as an anesthetic agent, has garnered attention for its rapid acting antidepressant properties, particularly in patients with treatment resistant depression (TRD). The compound's unique pharmacological profile primarily as an NMDA receptor antagonist has enabled its repositioning in psychiatric settings, where conventional antidepressants often fall short. This review delves into the evolving role of ketamine in psychiatry, examining its mechanisms of action, therapeutic applications, clinical efficacy, safety concerns, and emerging trends in the field. While ketamine therapy offers promise, its use raises ethical, regulatory, and long-term safety considerations that require continued research and careful implementation.

KEYWORDS

• Ketamine • Psychiatry • Depression • NMDA receptor • Antidepressant Treatment-resistant depression • Mental health • Suicidality • Glutamatergic system • Neuroplasticity

INTRODUCTION

Mental health disorders, especially major depressive disorder (MDD), have a profound impact on individuals and societies worldwide. Approximately 30% of individuals with MDD do not respond adequately to traditional antidepressant treatments, thereby falling into the category of treatment-resistant depression (TRD)[1]. The urgent need for innovative therapeutic options has prompted exploration into unconventional agents such as ketamine; a dissociative anesthetic with rapid antidepressant properties.

Ketamine's psychiatric applications mark a paradigm shift in treating mood disorders, offering symptom relief within hours

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rather than weeks, as seen with selective serotonin reuptake inhibitors (SSRIs). Initially developed as a phencyclidine derivative, ketamine's journey from battlefield anesthetic to psychiatric tool underscores the evolving understanding of depression's neurobiology.[2]

Aspect	Ketamine Therapy	Traditional Antidepressants
Mechanism of Action	NMDA receptor antagonist; enhances glutamate transmission and synaptic plasticity	Primarily monoamine-based (eg, SSRIs, SNRIs) enhancing serotonin, norepinephrine
Onset of Action	Rapid (within hours to 24 hours)	Delayed (2 to 6 weeks)
Duration of Effect	Short-acting; may require repeated infusions for sustained effect	Long-lasting with regular use
Efficacy in TRD*	High efficacy in treatment-resistant depression (TRD)	Lower response in TRD cases
Use in Suicidal Ideation	Proven rapid reduction in suicidal thoughts	Limited short-term efficacy in acute suicidality
Administration Route	IV, intranasal (esketamine), or oral (less common)	Oral (tablets or capsules)
FDA Approval	Esketamine (Spravato) approved for TRD and suicidal depression	Many approved antidepressants for MDD, anxiety disorders
Side Effects	Dissociation, dizziness, elevated blood pressure, nausea	Sexual dysfunction, weight gain, GI disturbances, insomnia
Addiction Potential	Moderate (especially with misuse or non-medical use)	Low addiction potential
Monitoring Needs	Requires in-clinic administration and monitoring post-dose	Less intensive monitoring; outpatient basis
Cost and Accessibility	Expensive; limited to specialized clinics	Widely available and more affordable
Therapeutic Use Beyond MDD	PTSD, OCD, bipolar depression (off-label)	Broad use in MDD, GAD, panic disorder, OCD, etc

PHARMACOLOGY OF KETAMINE

Chemical Composition and Isomers:

Ketamine is a racemic mixture comprising two enantiomers: S-(+)-ketamine and R-(-)-ketamine. The S-isomer, esketamine, is more potent in anesthetic and antidepressant effects, leading to its approval for psychiatric use in intranasal form[3].

MECHANISM OF ACTION

The primary mechanism through which ketamine exerts its antidepressant effects is antagonism of the N-methyl-D-aspartate (NMDA) receptor, a subtype of glutamate receptor.[4] This antagonism leads to increased synaptic glutamate release, activating AMPA receptors, which subsequently trigger downstream signaling pathways like BDNF (brain-derived neurotrophic factor) and mTOR (mammalian target of rapamycin), enhancing synaptogenesis and neuroplasticity.[5]

Additionally, ketamine influences opioid receptors, dopamine systems, and inflammatory pathways, contributing to its multifaceted psychiatric effects.[6]

THERAPEUTIC APPLICATIONS

Major Depressive Disorder (MDD):

Numerous clinical trials have validated ketamine's efficacy in alleviating depressive symptoms in MDD, especially among patients with TRD. A single intravenous infusion of ketamine has shown significant mood improvements within hours, with effects lasting up to one week.[7]

Suicidal Ideation:

Ketamine demonstrates rapid reduction of suicidal thoughts, making it a potentially life-saving intervention in acute settings. Studies report substantial decreases in suicidality within 24 hours post-infusion.[8] The rapid onset is crucial, especially during psychiatric emergencies.

Bipolar Depression:

While initial studies cautioned against ketamine use in bipolar disorder due to risk of mania, subsequent trials have shown it to be effective in the depressive phase, provided mood stabilizers accompany its use.[9]

Post-Traumatic Stress Disorder (PTSD)

Emerging evidence suggests ketamine may benefit individuals with PTSD. Its role in reducing trauma-related memories and improving mood has been explored in both military and civilian populations.[10]

Obsessive-Compulsive Disorder (OCD)

Pilot studies have indicated short-term symptom relief in OCD patients following ketamine infusion, although results are less robust than those for depression.[11]

ADMINISTRATION ROUTES AND DOSAGE

Intravenous (IV) Infusion

The most studied and widely used method is IV infusion, typically at a subanesthetic dose of 0.5 mg/kg over 40 minutes.[12] This route offers controlled administration and reliable absorption.

Intranasal Esketamine

Approved by the FDA in 2019, intranasal esketamine (Spravato) is used in conjunction with oral antidepressants for TRD. It provides a more convenient alternative but necessitates in-clinic administration due to potential side effects.[13]

Oral, Sublingual, and Intramuscular Routes

Other routessuch as oral, sublingual, or intramuscular (IM)are under investigation for homebased or broader applications, though bioavailability and consistency pose challenges.[14]

EFFICACY AND CLINICAL OUTCOMES

Onset and Duration

Unlike traditional antidepressants, ketamine acts within hours, offering quick symptom relief. However, effects are transient, often peaking within 24–48 hours and waning by 7–10 days, necessitating maintenance dosing.[15]

Response Rates

Studies report response rates of 50–70% in TRD patients following ketamine therapy, a marked improvement over conventional antidepressants in this group.[16]

Comparative Efficacy

Head-to-head trials comparing ketamine with ECT, SSRIs, and transcranial magnetic stimulation (TMS) suggest ketamine is non-inferior and, in many cases, preferred due to faster onset.[17]

SAFETY AND SIDE EFFECTS

Acute Side Effects

Common side effects include dissociation, euphoria, elevated blood pressure, nausea, and dizziness. These typically resolve within hours post-administration.[18]

Cognitive Effects

Concerns about cognitive impairment, particularly with long-term use, remain under investigation. Some studies report transient memory deficits, while others find no significant impact.[19]

Addiction and Abuse Potential

Ketamine's history as a recreational drug ("Special K") raises fears about addiction and misuse. However, when used in clinical settings under supervision, abuse risk is minimal.[20]

Bladder Toxicity

Prolonged high-dose exposure may cause ulcerative cystitis, though rare in therapeutic psychiatric use[21].

ETHICAL AND REGULATORY CONSIDERATIONS

Off-label Use

Much of ketamine's psychiatric application remains off-label, leading to variability in treatment protocols and legal oversight.[22]

Access and Cost

High costs, lack of insurance coverage, and limited certified clinics restrict patient access. The need for monitored administration adds logistical burdens.[23]

Consent and Vulnerable Populations

Due to its dissociative effects, informed consent is critical. Use in adolescents, elderly, and pregnant women is not yet well-established and should be approached cautiously.[24]

Ketamine Clinics and Integration into Practice

The rise of ketamine infusion clinics across North America, Europe, and Australia has

expanded access but introduced concerns regarding standardization, clinical oversight, and profit-driven models.[25]

Integration into mainstream psychiatry requires collaboration across disciplines, including psychopharmacology, nursing, and psychotherapy.

FUTURE DIRECTIONS AND RESEARCH

Biomarkers for Response

Ongoing research seeks to identify biomarkers that predict treatment response, such as EEG patterns, inflammatory markers, or genetic polymorphisms.[26]

Long-Term Safety Studies

Longitudinal studies are necessary to evaluate neurocognitive outcomes, bladder health, and addiction risk associated with long-term ketamine therapy.[27]

Combination Therapies

Ketamine may enhance outcomes when combined with CBT, mindfulness training, or other psychotropics, leveraging its neuroplasticity-promoting effects.[28]

Psychedelic Adjuncts

Interest is growing in pairing ketamine with psychedelic-assisted psychotherapy, viewing the dissociative state as a therapeutic window for deep psychological processing.[29]

ROLE OF THE NURSE IN KETAMINE THERAPY

Nurses play a vital role in the safe administration of ketamine therapy. They are responsible for pre-treatment assessment, monitoring vital signs, and ensuring patient safety during and after infusion. Nurses assess for dissociative symptoms, blood pressure changes, and psychological reactions, providing both emotional support and medical intervention if needed.[30] They also educate patients about the procedure, possible side effects, and post-treatment care.[31] Furthermore, nurses contribute to documentation, observe for adverse effects, and report to the psychiatrist or prescribing physician, making them essential to integrated care delivery in ketamine clinics.[32]

CONCLUSION

Ketamine therapy represents one of the most transformative developments in modern psychiatry. Its rapid onset and efficacy in treatment-resistant cases offer hope for many patients who previously had limited options. While its long-term safety and ideal delivery models are still being refined, ketamine's potential is undeniable. With rigorous research, ethical implementation, and patient-centered care, ketamine can become a cornerstone in the evolving psychiatric landscape.

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