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Review

Beyond Anesthesia: Ketamine's Expanding Role in Chronic Pain and Psychiatric Disorders

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Abstract

Objective: This review explores ketamine's expanding role in managing both chronic pain and mental health conditions, focusing on its pharmacologic mechanisms, clinical applications, and therapeutic potential. We assess its analgesic properties, FDA-approved application in the form of Spravato (esketamine) for depression, and off-label use for analgesia and psychiatric disorders. **Methods**: A systematic search of PubMed, Cochrane Library, and Scopus databases identified studies on ketamine's efficacy and safety in chronic pain and psychiatric disorders. The analysis included randomized controlled trials (RCTs), observational studies, and systematic reviews. **Results**: Ketamine has demonstrated significant efficacy in managing chronic pain in neuropathic pain, fibromyalgia, and complex regional pain syndrome (CRPS), especially in treatment-resistant cases. Mental health comorbidities are common in chronic pain populations, with up to 50% experiencing depression or anxiety. Ketamine's N-methyl-D-aspartate (NMDA) receptor antagonism not only underlies its analgesic effects but also contributes to rapid antidepressant responses in treatment-resistant depression (TRD) and acute suicidal ideation, as evidenced by its FDA-approved formulation, Spravato (esketamine). Beyond depression, emerging evidence supports ketamine's potential use in anxiety disorders, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and certain substance use disorders. However, its psychomimetic effects, safety concerns, and unclear long-term impact warrant careful clinical oversight. **Conclusion**: Ketamine presents a versatile therapeutic strategy for managing chronic pain and a wide range of mental health disorders, signifying its potential to bridge the gap in treatment-resistant cases. Ongoing research is needed to optimize dosing strategies, assess long-term safety, and integrate ketamine into multidisciplinary care models. This approach emphasizes personalized patient care and comprehensive monitoring to navigate the complexities of coexisting chronic pain and mental health challenges.

Keywords: ketamine; chronic pain; depression; treatment-resistant; anxiety disorders; N-methyl-D-aspartate (NMDA) receptors

1. Introduction

The intricate relationship between chronic pain and mental health disorders, notably anxiety and depression (A/D), poses significant challenges within the healthcare landscape. These conditions often coexist, compounding the burden on affected individuals and complicating treatment approaches [1].

Biologically, chronic pain and A/D share overlapping neural circuits, including the insular cortex, prefrontal cortex, anterior cingulate, thalamus, hippocampus, and amygdala. These regions are pivotal in both pain perception and emotional regulation [2]. The associated neuroinflammation and inflammatory cytokines further link these conditions, offering insights into their interconnected pathophysiology and potential targets for treatment [3]. Neuroinflammation and inflammatory cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α), contribute to the shared pathophysiology of chronic pain and mood disorders by driving neural sensitization and impaired emotional regulation. Ketamine's therapeutic effects may include modulating these pathways, as it reduces pro-inflammatory cytokines and enhances anti-inflammatory mediators, complementing its primary N-methyl-D-aspartate (NMDA) receptor modulation [4].

Clinically, the relationship between chronic pain and A/D is complex, as both are influenced significantly by subjective self-reports, making objective measurement challenging. They also share common determinants such as socio-economic factors, lifestyle influences like sleep and physical activity, and are exacerbated by social stigma and isolation [1]. Such complexities necessitate a holistic and multidimensional treatment approach.

Amid these challenges, ketamine emerges as a particularly promising agent due to its unique properties. Originally used as an anesthetic, ketamine has gained attention for its rapid-acting antidepressant effects and its ability to alleviate pain, making it a dual-purpose option for treating individuals with co-occurring chronic pain and A/D [5]. Research suggests that sub-anesthetic doses of ketamine can significantly improve symptoms in patients who have not responded to traditional treatments, offering new hope where other medications have failed [4]. Sub-anesthetic doses of ketamine effectively address both pain and mood symptoms. By modulating NMDA receptor activity, these doses reduce central sensitization and hyperalgesia while also providing rapid relief for treatment-resistant depression, acute suicidal ideation, and anxiety disorders.

Recent systematic reviews and clinical trials have begun to explore the efficacy of ketamine in these comorbid conditions. The findings indicate a potential reduction in both depression and pain symptoms, highlighting ketamine's role in managing complex cases of comorbidity [6]. However, the literature is still evolving, characterized by a mixture of outcomes and a need for more comprehensive, controlled studies to better understand the optimal use of ketamine, including dosing regimens, administration routes, and long-term effects [7].

The review explores ketamine's therapeutic potential in managing comorbid pain, anxiety, and depression, focusing on its effects in both chronic pain and mental health conditions. A systematic search of PubMed, Cochrane Library, and Scopus databases was conducted, prioritizing randomized controlled trials (RCTs), observational studies, and comprehensive reviews that address ketamine's impact on these conditions. The search included studies published from 2000 to the present to ensure the inclusion of relevant and contemporary evidence while excluding outdated findings, providing a robust foundation for evaluating ketamine's emerging clinical applications.

1.1 Historical Development and Early Applications of Ketamine

Ketamine, initially designated CI-581, emerged as a phencyclidine derivative and was first administered to humans in 1964, demonstrating dissociative anesthesia and effective pain relief at doses of 1 to 2 mg/kg [8]. Its development traces back to 1958 when phencyclidine (CI-395) showed promise but caused prolonged emergence delirium, leading researchers at Parke-Davis to explore alternatives [8].

Through innovative chemistry by V. Harold Maddox and pharmacologic studies by Graham Chen, ketamine was identified as a safer anesthetic. Human trials, led by Guenter Corssen in 1964, revealed its minimal adverse effects and unique side effects, such as floating sensations and limb numbness [8]. Ketamine received FDA approval in 1970, becoming a vital anesthetic during the Vietnam War due to its hemodynamic stability. Over the decades, ketamine has evolved beyond anesthesia, showcasing its potential in diverse therapeutic applications.

1.2 Clinical Indications and Therapeutic Applications of Ketamine

Ketamine hydrochloride is approved for general anesthesia, either alone or alongside other medications, and is effective for short-term procedures that do not require skeletal muscle relaxation [6]. It also serves as a pre-anesthetic and complements low-potency agents like nitrous oxide. In emergency settings, ketamine is valuable for procedural sedation and rapid sequence intubation, particularly in patients with bronchospasm due to its bronchodilatory properties [9].

Its applications include fracture reduction, dislocation management, and wound repair, especially in children, with dosing adjustments required for age-related metabolic differences [9]. Low-dose ketamine (LDK) has shown efficacy in managing severe pain from trauma, fractures, and other conditions, offering a safe alternative amid opioid concerns [10]. Off-label, it has been explored for depression and suicidal ideation alongside other antidepressants, though recreational use remains unapproved [11].

At sub-dissociative doses, ketamine provides analgesia and sedation, but exceeding critical thresholds intravenously (1–1.5 mg/kg) or intramuscularly (3–4 mg/kg) induces a dissociative state, distinct from traditional sedation protocols [9].

2. Methods

2.1 Literature Search Strategy

A systematic search was conducted across three major databases: PubMed, Cochrane Library, and Scopus, to identify relevant studies on the application of ketamine in the treatment of chronic pain and mental health disorders. The search was limited to studies published up to the present date. The keywords used in the search strategy included “ketamine”, “chronic pain”, “mental health disorders”, “depression”, “major depressive disorder”, “persistent depressive disorder”, “treatment-resistant depression (TRD)”, “anxiety”, “obsessive-compulsive disorder (OCD)”, “post-traumatic stress disorder (PTSD)”, “substance use disorders”, and “Spravato”. Boolean operators (AND, OR) were employed to combine search terms appropriately.

2.2 Inclusion and Exclusion Criteria

To ensure the relevance and quality of the included studies, the following inclusion criteria were applied:

- Study Types: Randomized controlled trials (RCTs), observational studies, and comprehensive reviews.
- Population: Patients diagnosed with chronic pain conditions and/or mental health disorders.
- Interventions: Studies involving the use of ketamine or its derivatives (e.g., esketamine) for therapeutic purposes.
- Outcomes: Studies reporting on the efficacy, safety, and therapeutic mechanisms of ketamine.

Studies were excluded if they:

- Were not published in peer-reviewed journals.
- Did not provide sufficient data on outcomes.
- Focused solely on the non-therapeutic use of ketamine (e.g., recreational use).
- Were not available in English.

2.3 Data Extraction and Synthesis

Data extraction was conducted systematically to ensure accuracy and relevance. The process involved multiple reviews of each study to confirm that the extracted information aligned with the study's stated objectives, methodologies, and outcomes. To enhance the reliability of this process, cross-referencing between the study text and its supplementary materials (e.g., tables, figures, and appendices) was performed wherever available. Additionally, data were synthesized through thematic analysis, grouping studies by their focus on chronic pain, mental health disorders, or overlapping conditions. This systematic approach aimed to mitigate potential bias by ensuring that all included data were verified against the predefined inclusion and exclusion criteria.

2.4 Quality Assessment

The quality of the included studies was assessed using standardized tools. For randomized controlled trials, the Cochrane Risk of Bias tool was employed to evaluate potential biases in study design, conduct, and reporting. Observational studies were assessed using the Newcastle-Ottawa Scale (NOS) for quality and risk of bias. Comprehensive reviews were evaluated based on predefined criteria for thoroughness and relevance.

2.5 Data Synthesis

The extracted data were synthesized qualitatively to provide a comprehensive overview of the current evidence on the use of ketamine for chronic pain and mental health disorders. Studies were grouped based on the primary condition being treated (chronic pain vs. mental health disorders) and the specific type of ketamine intervention used (e.g., IV ketamine, intranasal esketamine). Thematic analysis was conducted to identify common findings, discrepancies, and gaps in the literature.

2.6 Ethical Considerations

As this study involved a review of existing literature, no direct ethical approval was required. However, ethical considerations included ensuring the accurate representation of study findings and the acknowledgement of potential conflicts of interest in the reviewed studies.

2.7 Limitations

Potential limitations of this review include the variability in study designs and patient populations, which may affect the generalizability of the findings. Additionally, the relatively recent emergence of ketamine as a treatment modality means that long-term data are limited. Future research should address these gaps by focusing on larger, well-designed studies with extended follow-up periods.

By adopting this comprehensive and methodical approach, the review aims to provide a detailed and robust evaluation of ketamine's pharmacologic properties and its therapeutic potential for chronic pain and mental health disorders.

3. Pharmacokinetics of Ketamine

Ketamine, characterized by low plasma protein binding (10–30%) and high liposolubility, distributes extensively across body tissues with a central compartment volume of about 70 liters and a steady-state distribution volume of around 200 liters [6]. It is primarily metabolized in the liver through N-demethylation to form norketamine, which accounts for 80% of metabolites and is further processed into 6-hydroxy-norketamine before excretion; metabolism also occurs in the kidneys, intestines, and lungs, particularly in animals [12]. Ketamine is cleared from the body with a half-life of 2–3 hours, largely dependent on liver blood flow, and shows no enantiomer interconversion *in vivo*.

The metabolism involves several cytochrome P450 enzymes, not fully identified, which also get inhibited by ketamine potentially leading to tachyphylaxis with repeated use [13]. The S(+) isomer of ketamine is demethylated more rapidly than the R(-) isomer, resulting in faster clearance and larger distribution volume [14]. Norketamine, the main metabolite, appears rapidly in the bloodstream post-intravenous administration, acting as an analgesic at about 20–30% potency of ketamine and is eliminated slowly, influencing ketamine's dosage requirements during prolonged infusions [15].

Drug interactions can significantly alter ketamine metabolism; inducers like rifampin increase its clearance, while inhibitors like clarithromycin decrease it [16]. Different administration routes affect ketamine's bioavailability and pharmacokinetics, with intramuscular administration showing high bioavailability compared to oral routes, which are significantly reduced due to hepatic metabolism [17].

Renal and liver functions mildly influence ketamine pharmacokinetics, with noted alterations in patients with kidney dysfunction [18]. In pediatric populations, ketamine exhibits faster absorption and clearance than in adults, with adjustments needed in dosing particularly in the early months of life due to immature liver and kidney functions [9].

3.1 Pharmacokinetics of Ketamine: Routes of Administration and Bioavailability

Ketamine is administered via various routes, each influencing its pharmacokinetics and bioavailability differently. The primary routes of administration include intravenous (IV), intramuscular (IM), oral, sublingual, and subcutaneous, each presenting unique profiles in terms of absorption, distribution, metabolism, and elimination.

3.1.1 Intravenous (IV) Administration

○ Bioavailability: Nearly 100% because ketamine is directly delivered into the bloodstream, bypassing the first-pass hepatic metabolism.

○ Pharmacokinetics: With rapid onset (within 30 seconds), the plasma concentration reaches its peak quickly.

IV administration is favored for acute pain management, anesthesia induction, and in cases requiring fast, controlled delivery [6].

○ Effectiveness: IV ketamine is highly effective for anesthetic and analgesic purposes, maintaining a high plasma concentration, which results in reliable and predictable effects.

3.1.2 Intramuscular (IM) Administration

○ Bioavailability: Typically around 90%, IM administration offers high bioavailability as it avoids significant first-pass metabolism, though it is lower than IV administration due to slower absorption.

○ Pharmacokinetics: Absorption is slower than IV, typically reaching peak plasma concentrations in about 10 minutes [17]. IM ketamine also distributes rapidly through tissues due to its high lipophilicity.

○ Effectiveness: IM ketamine is highly effective, particularly in settings where IV access is unavailable. It is commonly used in anesthesia and pain management, including in emergency and pre-hospital care.

3.1.3 Subcutaneous Administration

○ Bioavailability: Similar to IM administration, offering around 90% bioavailability but with potentially slower absorption, depending on the injection site and individual variability.

○ Pharmacokinetics: Subcutaneous ketamine reaches peak plasma levels in about 10–15 minutes. This route is often used for sustained-release formulations in pain management.

○ Effectiveness: Subcutaneous ketamine is effective for pain management and sedation, providing a useful alternative when other routes are not feasible. It has been studied for chronic pain and treatment-resistant depression.

3.1.4 Sublingual Administration

○ Bioavailability: Higher than oral (~50–60%) since ketamine is absorbed through the mucosal membranes under the tongue, partially avoiding the first-pass effect.

○ Pharmacokinetics: The onset is faster than oral administration, with peak plasma concentrations occurring within 10–20 minutes. It provides a practical alternative to oral administration for outpatient use.

○ Effectiveness: Effective for analgesia and as part of psychiatric treatment, sublingual ketamine offers a good balance of bioavailability and convenience, with some studies suggesting comparable effects to oral doses for antidepressant and pain-relieving effects.

3.1.5 Oral Administration

○ Bioavailability: Significantly reduced (~20–30%) due to substantial first-pass metabolism in the liver, where ketamine undergoes N-demethylation to form the metabolite norketamine.

○ Pharmacokinetics: Following oral ingestion, ketamine is absorbed through the gastrointestinal tract, but much of it is metabolized before it reaches systemic circulation, leading to delayed onset (30 minutes to 1 hour).

○ Effectiveness: While oral ketamine can be effective, its lower bioavailability makes it less suitable for acute or emergency situations. However, it is used off-label for chronic pain management and as part of some treatment regimens for depression [17].

3.2 Route-Dependent Effects on Bioavailability and Efficacy

Research consistently demonstrates that the effectiveness of ketamine is influenced by its bioavailability, which varies significantly across routes of administration. IV and IM routes deliver higher concentrations of the drug to the bloodstream, leading to faster onset and more potent effects. In contrast, oral and sublingual routes involve slower absorption, leading to delayed effects and lower overall bioavailability, which may limit their use in acute settings.

Despite differences in bioavailability, ketamine's effectiveness across routes has been proven in both anesthetic and therapeutic contexts. Studies indicate that IM and IV ketamine are the preferred routes for anesthesia induction and pain management due to their rapid onset and high bioavailability [6]. Oral and sublingual ketamine are commonly explored in chronic pain management and psychiatric treatments, though higher doses or more frequent administration may be required due to their lower bioavailability [17].

4. Pharmacodynamics of Ketamine

Ketamine induces a unique state of "dissociative anesthesia", distinct from the anesthesia produced by drugs like barbiturates or propofol. In this state, patients may experience catalepsy with open eyes, nystagmus, and preserved reflexes such as laryngeal and corneal, allowing for surgical procedures without motor responses to pain [8]. In terms of neurophysiology, ketamine creates a dissociation between the thalamic-neocortical and limbic systems, allowing sensory inputs to reach cortical areas without integration in some associative regions [15].

Functional MRI studies have shown that ketamine at plasma concentrations reducing pain also decreases activity in the insular cortex and thalamus, areas typically activated by pain [3]. Subanesthetic doses of ketamine reduce cerebral activation in response to painful stimuli, affecting regions associated with the affective components of pain, such as the secondary somatosensory cortex, insula, and anterior cingulate cortex [10].

Ketamine's effects on the electroencephalogram (EEG) are also notable; unlike other anesthetics, it reduces alpha rhythm amplitude without altering frequency and introduces theta waves. These EEG changes do not directly correlate with the depth of anesthesia [19]. Additionally, ketamine's supraspinal actions are predominant, but its spinal actions—blocking afferent signals from the spino-reticular pathways—are significant as well [20].

The relationship between ketamine doses and their effects includes disruptions in memory at 70 ng/mL and the induction of lateral nystagmus at 200 ng/mL [12]. The effective dose (ED50) for inducing a non-responsive state to verbal cues is between 0.4 and 0.7 mg/kg, with higher doses needed for complete anesthesia. Steady-state plasma concentrations for analgesic effects start from 100 ng/mL, increasing following peripheral nerve injury [10].

Psychodysleptic effects, or psychedelic phenomena, occur predominantly during the emergence phase from anesthesia, characterized by sensory perception disturbances, mood changes, and depersonalization. These effects can start at concentrations as low as 50 ng/mL, with more severe symptoms such as anxiety and paranoia at around 500 ng/mL [14].

Studies also highlight ketamine's potential antidepressive properties, rapidly alleviating symptoms like suicidal ideation and improving postoperative mood in depressed patients. This is attributed to its effects on the NMDA receptors, which are integral to both the pathophysiology of depression and the modulation of glutamatergic neurotransmission [4].

5. Mechanisms of Action

Ketamine's neuropharmacology is multifaceted, primarily targeting glutamate receptors, including NMDA and non-NMDA types. The antagonism of NMDA receptors is fundamental to ketamine's distinctive effects such as amnesia, altered sensory perception, analgesia, and neuroprotection [6]. Figs. 1,2,3 provide a detailed structural representation of ketamine at the NMDA receptor, illustrating its subunits, key binding sites, and the role of magnesium in channel blockade, which underpins many of ketamine's pharmacological effects.

5.1 Glutamate-Independent Mechanisms

Ketamine affects multiple receptor systems, including opioid, monoaminergic, cholinergic, nicotinic, and muscarinic receptors. Its interaction with γ-Aminobutyric acid (GABA), the primary inhibitory neurotransmitter, enhances GABAergic inhibition through the GABA-A receptor complex. Although this interaction contributes to general anesthetic properties, it does not significantly account for ketamine's analgesic effects, except at very high concentrations [12].

Ketamine's affinity for opioid receptors varies, with the S(+) isomer showing 2–3 times higher affinity than the R(-) isomer. Despite this, the analgesic effects of ketamine are not reversed by opioid antagonists like naloxone or naltrexone, suggesting other mechanisms at play, though some psychic effects may be mediated through kappa opioid receptors [15].

The monoaminergic system's modulation is crucial, where ketamine enhances the activity of noradrenergic neurons and blocks the reuptake of catecholamines, leading to a hyperadrenergic state with increased norepinephrine, dopamine, and serotonin in circulation. Fig. 1 complements this discussion by illustrating ketamine's metabolic pathways, highlighting its transformation into norketamine and hydroxy-norketamine, which are implicated in some of its prolonged effects.

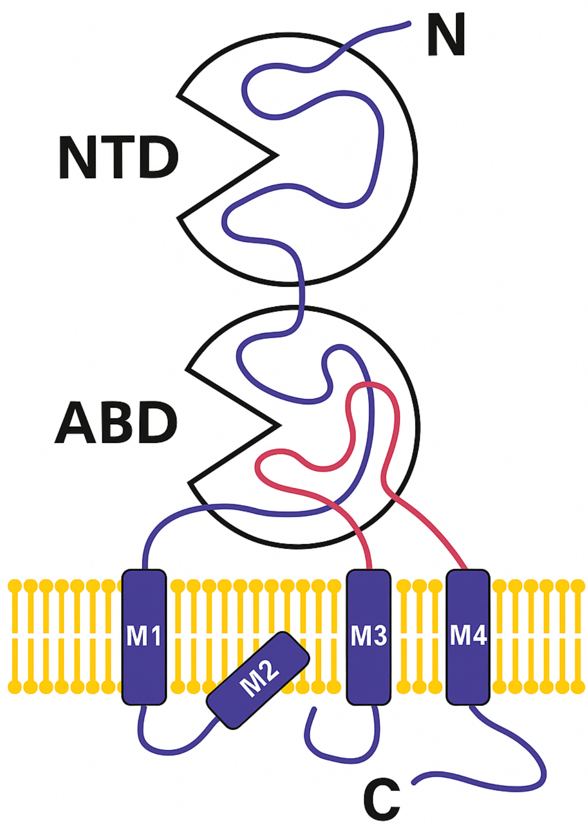

Fig. 1. Structure of the four subunits of the NMDA receptor. NTD, N-terminal domain; ABD, agonist-binding domain; NMDA, N-Methyl-D-Aspartate. The M2 segment faces the cytoplasm and would be the receptor ion channel.

In regions like the hippocampus and striatum, ketamine's impact on cholinergic neurons inhibits acetylcholine release, significantly influencing psychic phenomena. An anticholinesterase agent, physostigmine, can reverse these effects, differentiating between ketamine's sedative and analgesic properties [14]. Ketamine also interacts with the purinergic system, affecting the urinary tract, and modifies ion channel activities, including sodium, L-type calcium, and potassium channels. These interactions confer local anesthetic properties, comparable to lidocaine, and contribute to its neuroprotective properties in the S(+) isomer. Fig. 2 illustrates the structural dynamics of these ion channels and their modulation by ketamine, including its effects on calcium and sodium conductance.

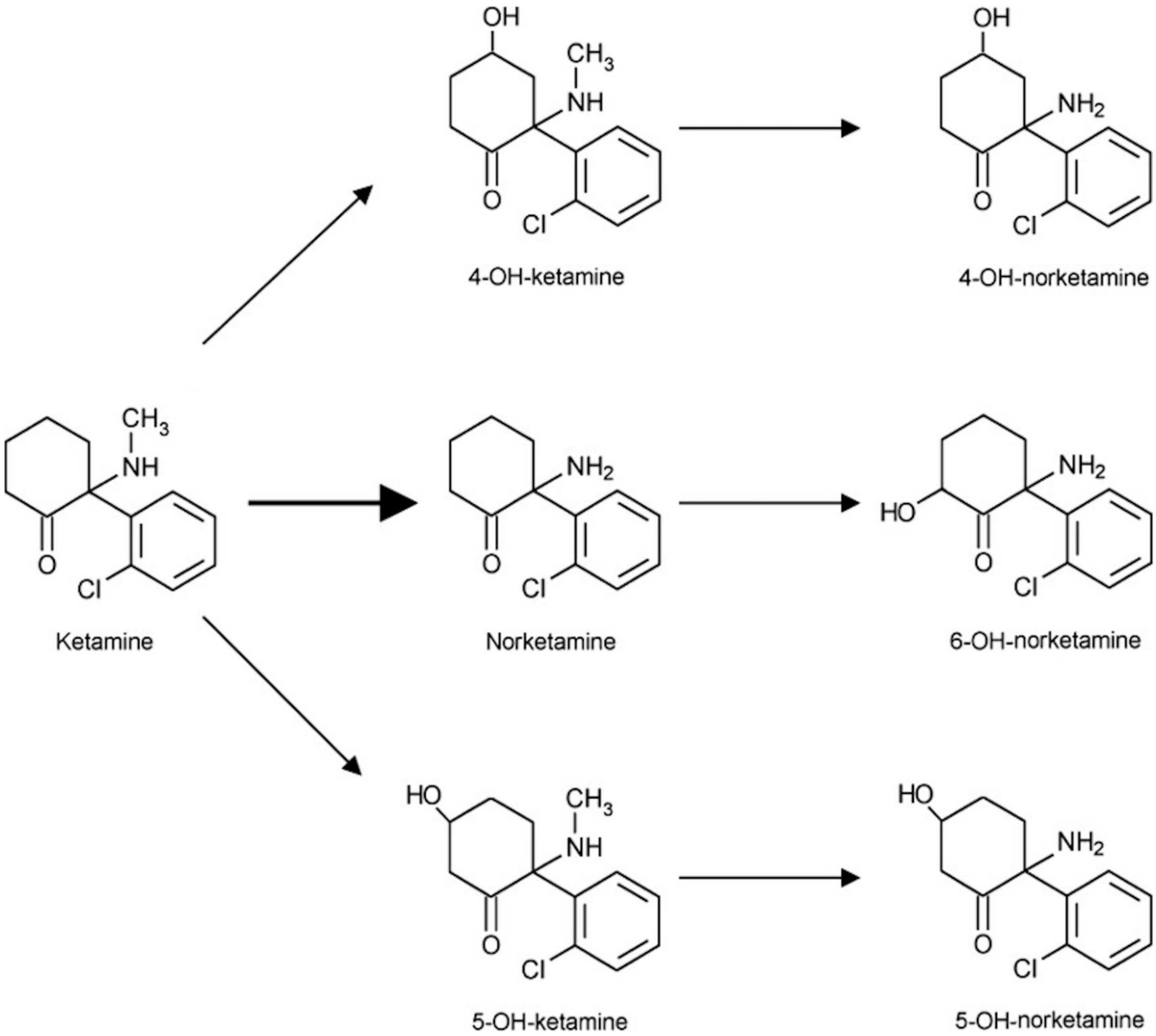

Fig. 2. Metabolism. Ketamine is metabolized mainly to norketamine (80%), itself secondarily transformed into hydroxy-norketamine (15%), mainly 6-hydroxy-norketamine. Accessory pathway passes directly through the transformation of ketamine in hydroxy-ketamine (5%).

5.2 Glutamate-Dependent Mechanisms

5.2.1 NMDA Receptor Dynamics

The NMDA receptor, selectively inhibited by ketamine at concentrations ranging from 2 to 50 µm, is central to many of ketamine's critical effects, including analgesia, amnesia, and neuroprotection [6]. Fig. 3 provides an in-depth visual depiction of the receptor's structural and functional dynamics, showing how magnesium ions block the channel under resting conditions and how ketamine binds to the PCP site to inhibit calcium influx.

Glutamate, the most abundant neurotransmitter in the CNS, activates ionotropic receptors like NMDA, AMPA, and kainate. These receptors play a pivotal role in neurotransmission and are highly concentrated in areas associated with pain processing, such as the spinal dorsal horn [14]. Upon glutamate release, it binds to these receptors, causing ion channels to open and leading to membrane depolarization. NMDA receptors are uniquely permeable to calcium, a property influenced by their tetrameric structure comprising NR1 and NR2 subunits, as detailed in Fig. 3.

5.2.2 Magnesium Channel Block

The voltage-dependent magnesium block is the primary regulatory mechanism controlling the NMDA receptor's activity. At a resting membrane potential of –70 mV, magnesium ions obstruct the receptor channel even when glutamate and glycine are bound. Fig. 3 illustrates this interaction, showing how membrane depolarization removes magnesium, permitting calcium influx. This mechanism synergizes with ketamine's action, enhancing the analgesic and anesthetic effects when combined with magnesium therapy [8].

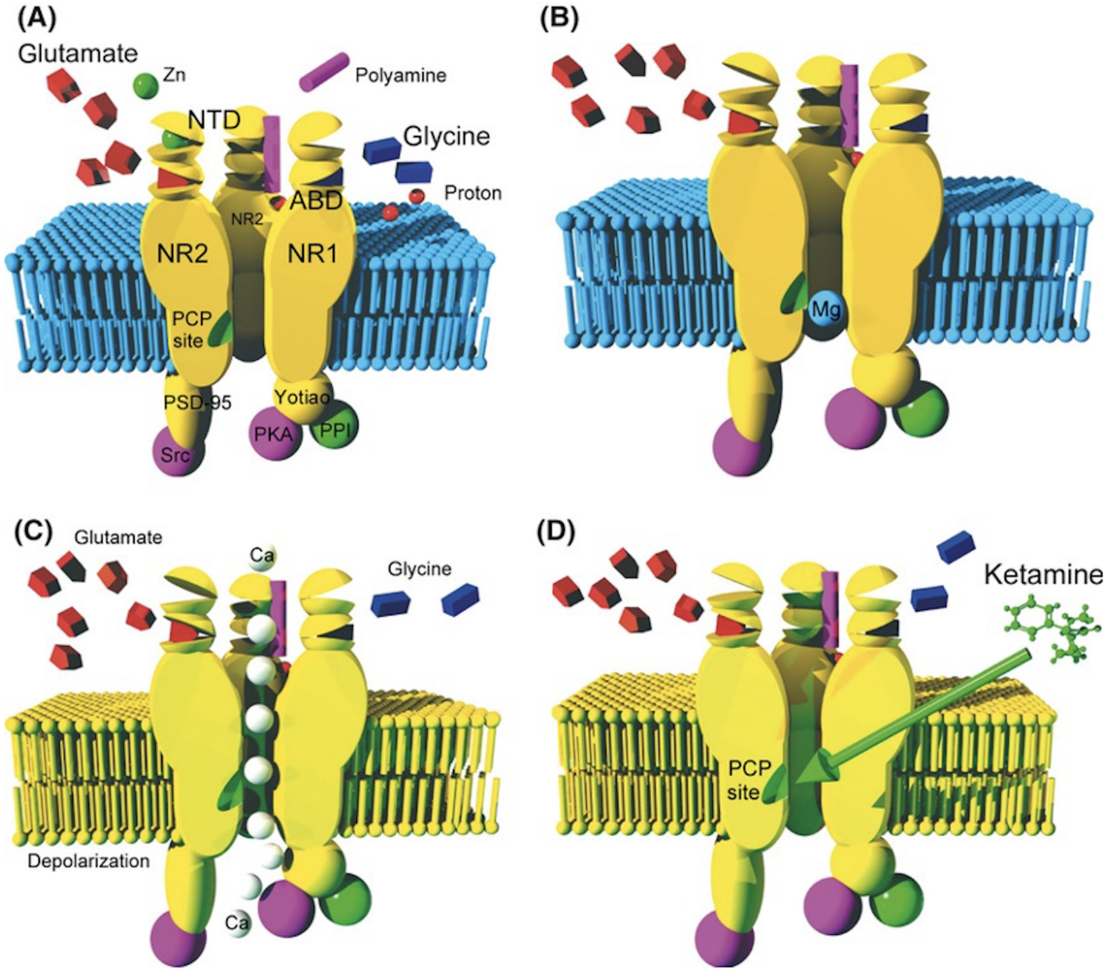

Fig. 3. Structure and inhibition of NMDA receptors by ketamine. Illustrates the structure and function of the NMDA receptor, which consists of two NR1 and two NR2 subunits. These subunits form a cation-selective channel anchored to the membrane via the PSD-95 protein and linked to Src tyrosine kinase. The receptor has key binding sites: glutamate binds to the NR2 subunit at the ABD domain, and glycine binds to the NR1 subunit as a co-agonist. When the membrane is not depolarized, magnesium ions (Mg^{2+}) block the channel by occupying a binding site near the intracellular part of the receptor. Upon membrane depolarization, Mg^{2+} is released, allowing the influx of calcium ions. Additionally, zinc binds to the NTD domain of the NR2 subunit, and protons regulate the receptor's closed state. The site for polyamines is less defined but is believed to be near the ABD domain. Ketamine and related compounds bind to the PCP site, overlapping the magnesium binding site, blocking the channel and preventing its activation, even in the presence of glutamate and glycine. (A) NMDA receptor structure and key binding sites. The NMDA receptor is a tetramer composed of two NR1 and two NR2 subunits. It is anchored to the membrane via PSD-95 and linked to intracellular kinases such as Src. Glutamate binds the NR2 subunit at the ABD, while glycine binds the NR1 subunit as a co-agonist. Zinc binds to the NTD of NR2, and protons regulate the receptor's closed state. Polyamine interaction sites are suggested near the ABD region. (B) Channel blocked by magnesium at resting potential. In the absence of membrane depolarization, Mg^{2+} ions bind within the channel pore near the intracellular side, preventing ion conductance even in the presence of glutamate and glycine. (C) Channel activation upon depolarization. Depolarization of the membrane displaces Mg^{2+}, allowing Ca^{2+} influx through the open channel. This influx is essential for downstream signaling and synaptic plasticity. (D) Inhibition by ketamine. Ketamine binds to the phencyclidine (PCP) site within the NMDA receptor channel, overlapping with the Mg^{2+} binding region. This noncompetitive antagonism blocks ion flow, preventing activation even when glutamate and glycine are bound.

5.2.3 Receptor Phosphorylation and Allosteric Modulation

Phosphorylation of the NMDA receptor, regulated by proteins such as PP1 and PKA, influences its activation and response to hyperalgesia. The structural details in Fig. 3, including the receptor's interaction with scaffolding proteins like PSD-95, provide a framework for understanding how ketamine modulates these processes. Additionally, zinc and protons act as allosteric modulators, stabilizing the receptor in a closed state under specific conditions, as depicted in Fig. 3.

6. Ketamine Infusions for the Treatment of Chronic Pain

Ketamine's role in chronic pain management has become a focal point of research, reflecting its potential and complexities. This synthesis of recent studies delineates its efficacy, optimal administration routes, and associated adverse effects, providing a comprehensive understanding of its utility in chronic pain treatment.

A year-long observational study involving 256 patients with refractory chronic pain revealed a significant reduction in pain intensity from a baseline of 6.8 to 5.7 on the numerical pain rating scale [5]. This study identified three distinct pain trajectories: mild (16% of patients, mostly with neuropathic pain), moderate (35.3%), and severe (45.7%, primarily with fibromyalgia). The findings indicated that ketamine's efficacy was influenced by the type of pain and associated conditions like anxiety, depression, and quality of life. Despite the promising results, the study underscored the need for further research to optimize patient subtyping and treatment protocols to enhance ketamine's efficacy and safety profile. Adverse events were common initially but decreased over time, suggesting a potential acclimatization effect.

A meta-analysis of six RCTs involving 195 patients scrutinized ketamine's effectiveness in chronic non-cancer pain. The primary outcome, pain relief at four weeks, was not significantly achieved (MD = –1.12), but ketamine showed efficacy at one, two, eight, and twelve weeks [21]. This temporal variation suggests that ketamine may have a delayed or sustained effect in some patients. However, the increased incidence of psychedelic side effects, such as hallucinations and dissociative symptoms, raised concerns about its tolerability. The meta-analysis highlighted the heterogeneity in study designs, dosages, and administration routes, which complicates the formulation of standardized treatment guidelines. The trial sequential analysis indicated that the meta-analysis might be underpowered, emphasizing the need for larger, well-designed trials to confirm these findings and refine dosing regimens.

A comprehensive review of ketamine's application in various chronic pain conditions, including central pain, CRPS, fibromyalgia, ischemic pain, and nonspecific neuropathic pain, found level II evidence supporting ketamine's efficacy in central pain and fibromyalgia, where it reduced pain intensity, tenderness, and increased endurance [1]. For CRPS, only level IV evidence was available, primarily from case reports, which limits the generalizability of the findings. In ischemic pain, ketamine showed a potent, dose-dependent analgesic effect but with a narrow therapeutic window. The review underscored the variability in ketamine's effectiveness across different conditions and emphasized the need for controlled studies to better define its role in chronic pain management. The frequent occurrence of adverse effects, particularly at higher doses, further complicates its use as a long-term treatment option.

A synthesis of data from multiple systematic reviews highlighted the robust evidence supporting ketamine's efficacy in reducing postoperative pain scores and opioid requirement [22]. However, the evidence for its use in chronic non-cancer pain remained limited and inconsistent. The review emphasized that while ketamine can provide substantial pain relief in some cases, its long-term safety profile is unclear, particularly with repeated infusions. The adverse effects, which are dose-dependent, include psychotomimetic symptoms, nausea, dizziness, and in some cases, serious effects like hepatotoxicity and cystitis. The review pointed out that spinal administration of ketamine is associated with neurotoxicity, and oral administration has low bioavailability with a high rate of adverse effects, making these routes less desirable. The evidence supported the cautious use of low-dose ketamine as an adjuvant to opioids, particularly in refractory cancer pain or palliative care settings, where the risk-benefit ratio may be more favorable.

7. Intranasal Esketamine for the Treatment of Major Depressive Disorder and Other Psychiatric Conditions with Pain-Related Comorbidities

7.1 Intranasal Esketamine

Esketamine, the S-enantiomer of ketamine, has emerged as a novel and promising treatment for various psychiatric and pain-related conditions. Administered intranasally, esketamine offers several advantages, including rapid absorption and quick onset of action, which are particularly beneficial for patients requiring urgent relief from symptoms. This section aims to provide a comprehensive review of the pharmacologic properties, clinical applications, and recent research findings related to intranasal esketamine.

7.2 Pharmacologic Properties and Mechanism of Action

Intranasal esketamine functions as an N-methyl-D-aspartate (NMDA) receptor antagonist, modulating glutamate neurotransmission critical for mood regulation and pain perception. This mechanism underpins its rapid antidepressant effects, often evident within hours compared to the weeks required for traditional antidepressants [5]. Nasal administration bypasses first-pass metabolism, ensuring higher bioavailability than oral delivery, while being less invasive and more convenient than intravenous routes, thus improving patient adherence. Rapid absorption through the nasal mucosa allows for a quick onset, making esketamine particularly beneficial for treatment-resistant depression and acute suicidal ideation. Moreover, esketamine enhances synaptic plasticity and neurogenesis in key regions like the prefrontal cortex and hippocampus, further supporting its therapeutic effects [4].

Esketamine's pharmacologic profile extends beyond NMDA receptor antagonism. By reducing hyperactive glutamatergic signaling, a hallmark of chronic pain and mood disorders, esketamine promotes synaptic plasticity in critical brain regions such as the prefrontal cortex, hippocampus, and anterior cingulate cortex, which are central to emotional regulation and pain perception. On a neuronal level, it primarily targets glutamatergic neurons within cortical and limbic circuits, alleviating central sensitization linked to chronic pain while enhancing connectivity that contributes to depression relief.

Recent research highlights ketamine-induced neurogenesis and the activation of downstream pathways such as the mammalian target of rapamycin (mTOR), contributing to its rapid and sustained antidepressant effects [12]. Additionally, its interaction with other neurotransmitter systems enhances its therapeutic versatility. For instance, esketamine's modulation of μ-opioid receptors supports its pain-relieving properties [20], while its impact on serotonin and dopamine neurotransmission reinforces its efficacy in treating mood disorders [21].

These mechanisms collectively emphasize esketamine's ability to address both nociceptive and emotional dysregulation pathways, making it a unique and valuable therapeutic option for treatment-resistant conditions. Its combined effects on NMDA receptors, synaptic plasticity, and neurotransmitter systems highlight its dual role in alleviating chronic pain and depression, advancing its potential as a transformative tool in managing complex coexisting conditions.

7.3 Clinical Applications

7.3.1 Treatment-Resistant Depression (TRD)

Intranasal esketamine has been approved by the FDA for use in adults with TRD, representing a significant advancement in psychiatric care. Traditional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), often fail to provide adequate relief for many patients. Clinical trials have demonstrated that esketamine, when used in conjunction with an oral antidepressant, significantly reduces depressive symptoms in patients who have not responded to other treatments [11]. Specifically, studies have found that patients treated with esketamine showed a rapid reduction in depressive symptoms, with significant improvements noted as early as 24 hours post-administration [11]. This rapid onset of action is critical for individuals at high risk of suicide or severe functional impairment.

7.3.2 Chronic Pain Management

Beyond its psychiatric applications, esketamine has shown promise in the management of chronic pain conditions. Its analgesic effects are attributed to the blockade of NMDA receptors, which play a crucial role in the central sensitization and hyperalgesia associated with chronic pain [6]. Studies have reported that intranasal esketamine can provide substantial pain relief in conditions such as complex regional pain syndrome (CRPS) and neuropathic pain [10]. Additionally, esketamine's efficacy in reducing opioid consumption among chronic pain patients has been a significant finding, highlighting its potential role in addressing the opioid crisis [23].

7.3.3 Anxiety and Comorbid Conditions

The therapeutic potential of esketamine extends to the treatment of anxiety disorders and other comorbid conditions. Research indicates that esketamine may reduce symptoms of generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD), likely due to its rapid modulation of glutamatergic pathways and enhancement of synaptic plasticity [24]. In one study, patients with treatment-resistant GAD showed significant improvements in anxiety symptoms within hours of receiving intranasal esketamine [24]. Furthermore, another study reported that a single infusion of esketamine led to sustained reductions in PTSD symptoms, suggesting its potential as a rapid-acting treatment for severe anxiety disorders [25].

7.4 Most Recent Research Findings

Recent studies have focused on optimizing the dosing regimens, safety profiles, and long-term efficacy of intranasal esketamine. Clinical trials have demonstrated that esketamine, combined with an oral antidepressant, led to a statistically significant improvement in depressive symptoms compared to placebo [11]. Similarly, long-term studies have highlighted the sustained benefits of esketamine over a year-long treatment period, emphasizing its potential for long-term management of TRD [26]. These findings are supported by additional research showing that maintenance therapy with esketamine can prevent relapse in patients with TRD [26].

In terms of safety, intranasal esketamine is generally well-tolerated, with the most common side effects being transient dissociation, dizziness, and nausea [27]. These side effects are typically mild to moderate in severity and tend to diminish with continued use. Importantly, the dissociative effects of esketamine are usually short-lived and resolve within 1–2 hours post-administration, allowing patients to return to normal activities shortly after treatment [23].

7.5 Overall

Intranasal esketamine represents a groundbreaking advancement in the treatment of chronic pain, mental health issues, and other associated comorbidities. Its rapid onset of action and unique mechanism of targeting NMDA receptors make it a valuable therapeutic option for patients with treatment-resistant conditions. Ongoing research continues to elucidate its full potential and optimal use in clinical practice, promising a brighter future for those suffering from debilitating psychiatric and pain disorders.

8. Discussion

The multifaceted pharmacologic properties of ketamine and its applications in chronic pain management, mental health disorders, and associated comorbidities highlight both its therapeutic potential and challenges. This discussion synthesizes key findings, focusing on the nuances of ketamine's clinical utility.

8.1 Chronic Pain Management

Ketamine has demonstrated efficacy in chronic pain management, particularly for cases refractory to standard treatments. A study of 256 patients reported significant pain reduction, with improvements most notable in neuropathic pain and fibromyalgia [5]. The study emphasized the importance of addressing associated psychological factors like anxiety and depression, while noting that adverse events often diminished over time with proper monitoring.

A meta-analysis identified ketamine's benefits at various time points for chronic non-cancer pain, despite limited primary outcomes at four weeks [23]. These findings underscored the need for well-designed trials to refine treatment protocols, given the variability in dosing and administration routes.

Additional reviews have further validated ketamine's role in specific conditions. Evidence supports ketamine's efficacy in central pain and fibromyalgia, while other findings highlight its ability to reduce postoperative pain scores and opioid requirements [1,22]. However, the inconsistent evidence for chronic non-cancer pain and frequent adverse effects, such as psychotomimetic symptoms and hepatotoxicity, necessitate cautious, individualized use.

Integration of Clinical Practice Guidelines: The American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines provide a structured approach to ketamine use in chronic pain management. They recommend low-dose ketamine infusions (0.1–0.5 mg/kg/hour) as a third-line treatment for refractory pain, emphasizing controlled settings and monitoring to minimize adverse effects. Pre-treatment evaluations are essential to screen for contraindications, including cardiovascular instability, psychosis, or substance use disorders. These guidelines further highlight the need for periodic reassessment of efficacy and safety during long-term use, offering a practical framework for clinical application.

Collectively, these studies and guidelines highlight the need for careful patient selection, personalized treatment plans, and rigorous trials to establish optimal dosing, administration routes, and strategies to mitigate adverse effects. Ketamine's utility in chronic pain management remains significant, but further research is essential to address its limitations and optimize its clinical application.

8.2 Mental Health Disorders

Beyond pain management, ketamine has shown significant promise in treating various mental health disorders, particularly treatment-resistant depression (TRD). The rapid antidepressant effects of ketamine, often observed within hours of administration, represent a significant advancement over traditional antidepressants, which may take weeks to show effects [11,27].

The therapeutic potential of ketamine extends to anxiety disorders, OCD, PTSD, and certain substance use disorders. Several cohorts of patients followed over time showed significant improvements in anxiety and PTSD symptoms following ketamine administration, likely due to its modulation of glutamatergic pathways and enhancement of synaptic plasticity. These findings underscore ketamine's potential as a rapid-acting treatment for severe anxiety disorders and comorbid conditions, offering new hope for patients who have not responded to conventional therapies [24,25].

Clinical Practice Guidelines and Application Framework: The American Psychiatric Association (APA) guidelines recommend intranasal esketamine (Spravato) as an adjunct to oral antidepressants for TRD, emphasizing a phased approach beginning with an induction period (twice weekly for four weeks) followed by maintenance therapy. The guidelines stress the importance of patient monitoring during administration due to potential dissociative symptoms and transient hypertension. Off-label intravenous ketamine, while showing promise in some studies, is recommended only in specialized settings with informed patient consent, given the lack of robust long-term evidence.

Recent research has focused on optimizing dosing regimens, safety profiles, and long-term efficacy of intranasal esketamine. Studies have highlighted the sustained benefits of esketamine over a year-long treatment period, emphasizing its potential for long-term management of TRD [11,26]. These findings support the integration of esketamine into clinical practice, particularly for patients at high risk of suicide or severe functional impairment.

The integration of clinical practice guidelines into ketamine's application for chronic pain and mental health conditions bridges the gap between research findings and actionable clinical strategies. These guidelines provide clarity on patient selection, treatment protocols, and safety monitoring, ensuring the effective and responsible use of ketamine in diverse clinical settings. Continued research and adherence to evidence-based frameworks are crucial for optimizing ketamine's therapeutic potential while mitigating its risks.

9. Conclusion and Limitations

Ketamine, with its unique pharmacologic properties and multifaceted mechanisms of action, stands as a promising therapeutic agent in the realm of chronic pain management and mental health disorders. Its efficacy in reducing pain and alleviating symptoms of treatment-resistant depression (TRD), anxiety, PTSD, and certain substance use disorders underscores its potential as a versatile treatment option. The rapid onset of action, especially in TRD, offers a significant advantage over traditional treatments, providing swift relief for patients in acute distress. Moreover, the FDA approval of intranasal esketamine (Spravato) marks a milestone in psychiatric care, validating the clinical benefits of ketamine's rapid antidepressant effects.

However, the therapeutic use of ketamine is accompanied by challenges that necessitate careful consideration. The variability in patient response, the high incidence of adverse effects, and the need for personalized treatment protocols highlight the complexity of integrating ketamine into clinical practice. The potential for serious side effects such as psychotomimetic symptoms, hepatotoxicity, and cystitis calls for vigilant monitoring and tailored dosing strategies. Despite these challenges, the accumulating evidence supports ketamine's role as a third-line treatment for refractory cases, particularly when conventional therapies fail to provide adequate relief.

9.1 Study Limitations

1. Heterogeneity in Study Designs: The variability in study designs, patient populations, dosing regimens, and administration routes across existing research complicates the ability to draw definitive conclusions. Standardized methodologies in future studies will improve comparability and reliability of results.

2. Adverse Effects: The high incidence of adverse effects, particularly at higher doses, remains a significant limitation. Strategies to mitigate these effects, such as adjunctive medications or alternative dosing schedules, need to be explored.

3. Limited Long-Term Data: The lack of long-term safety and efficacy data limits the ability to fully understand the implications of chronic ketamine use. Future research must address this gap to ensure the safe and sustainable application of ketamine in clinical practice.

4. Ethical and Regulatory Challenges: The potential for abuse and the need for controlled administration present ethical and regulatory challenges. Developing clear guidelines and protocols for the clinical use of ketamine will be essential to balance its therapeutic benefits against the risks of misuse.

5. Patient Selection: Identifying the patients who are most likely to benefit from ketamine therapy remains a challenge. Developing robust criteria for patient selection, based on clinical and demographic factors, will enhance the effectiveness and safety of treatment.

9.2 Future Directions

1. Refinement of Dosing Strategies: Future research should focus on identifying optimal dosing regimens for different conditions. This includes determining the most effective doses that maximize therapeutic benefits while minimizing adverse effects. Studies should explore the dose-response relationship and the impact of various administration routes, such as intravenous, intranasal, and oral, on efficacy and safety.

2. Long-Term Safety and Efficacy: Longitudinal studies are needed to assess the long-term safety and efficacy of ketamine. Given the potential for serious side effects and the lack of extensive long-term data, it is crucial to monitor patients over extended periods to understand the full impact of chronic ketamine use.

3. Mechanistic Studies: Further research into the molecular and cellular mechanisms underlying ketamine's therapeutic effects will enhance our understanding of its action. This includes exploring the role of NMDA receptor antagonism, glutamatergic modulation, and interactions with other neurotransmitter systems in pain and mood regulation.

4. Personalized Medicine: The development of personalized treatment protocols based on patient-specific factors such as genetic markers, pain type, and psychological comorbidities could optimize ketamine therapy. Identifying biomarkers that predict response to ketamine will allow for more targeted and effective treatments.

5. Integration into Multimodal Therapies: Investigating the integration of ketamine into multimodal treatment approaches, including its combination with other pharmacological agents and non-pharmacological therapies, could enhance overall treatment outcomes. Combining ketamine with cognitive-behavioral therapy, physical rehabilitation, or other interventions may provide synergistic benefits.

In conclusion, ketamine represents a significant advancement in the treatment of chronic pain and mental health disorders. Its rapid-acting and multifaceted therapeutic effects offer new hope for patients with treatment-resistant conditions. However, the integration of ketamine into clinical practice must be approached with caution, ensuring thorough research and careful consideration of individual patient needs. By addressing the current limitations and focusing on future research directions, the medical community can harness the full potential of ketamine, improving the quality of life for countless individuals suffering from chronic pain and mental health challenges.

Author Contributions

Conceptualization, methodology, investigation, data analysis, writing—original draft preparation, and writing—review and editing were all conducted by CZ. The author has read and approved the final manuscript. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

While AI tools were utilized for grammar and punctuation refinement, the content represents original research and synthesis conducted by the author.

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