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KETAMINE AS AN OPTIONAL TREATMENT IN CHRONIC PAIN - A REVIEW

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ABSTRACT

Chronic pain is a pervasive and debilitating condition that affects millions of individuals worldwide. Traditional methods of pain management, including the use of opioids, often fall short in providing adequate relief and come with significant risks, such as dependency and tolerance. As a result, there has been growing interest in exploring alternative treatments, with ketamine emerging as a promising option. Ketamine, a dissociative anesthetic, has shown potential in alleviating various types of chronic pain, including neuropathic pain, cancer-related pain, and pain associated with complex regional pain syndrome (CRPS).

Aim of study: This review aims to examine the current evidence on the efficacy of ketamine in chronic pain management, exploring its mechanisms of action, clinical applications, safety profile, and potential limitations.

Methods and materials: PubMed and Scopus databases were used to search for topic treated articles.

KEYWORDS

Ketamine, Chronic Pain, Ketamine Treatment in Chronic Pain, Pain, Ketamine Mechanism of Action

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Introduction

Chronic pain is a pervasive and debilitating condition that affects millions of individuals worldwide[1]. Traditional methods of pain management, including the use of opioids, often fall short in providing adequate relief and come with significant risks, such as dependency and tolerance[32]. As a result, there has been growing interest in exploring alternative treatments, with ketamine emerging as a promising option. Ketamine a substance introduced in 1964 as a dissociative anesthetic[5] that has shown potential in alleviating various types of chronic pain, including neuropathic pain, cancer-related pain, and pain associated with complex regional pain syndrome (CRPS). Recently, there has been a growing trend in using ketamine at very low doses to provide pain relief across a variety of acute and chronic pain conditions. This approach relies on ketamine's antagonistic effect on the N-methyl-D-aspartate (NMDA) receptor, which is a ligand-gated calcium channel primarily activated by the neurotransmitter glutamate. Since the activation of this calcium channel plays a significant role in the 'wind-up' phenomenon that results in central sensitization, it is believed that ketamine could be particularly effective in treating 'pathological' pain states that arise from this process[6]. This review aims to examine the current evidence on the efficacy of ketamine in chronic pain management, exploring its mechanisms of action, clinical applications, safety profile, and potential limitations.

Chronic pain

Chronic pain, defined as pain persisting for more than three months, represents a significant health challenge with profound effects on patients' quality of life[1]. Chronic pain is a complex and widespread condition, impacting approximately one in five people globally. It accounts for more than 15% of all medical consultations and significantly impairs both quality of life and emotional health. [32]. It is recognized as a complex condition that can arise from various causes, including tissue damage, neurological disorders, and inflammatory processes. Literature sourced from PubMed emphasizes that chronic pain is not merely an extension of acute pain but rather a distinct clinical entity, often associated with long-term alterations in both the central and peripheral nervous systems. Systematic reviews and meta-analyses highlight the crucial role of NMDA receptor dysfunction and changes in neurotransmitter expression, such as glutamate and substance P, in the pathophysiology of chronic pain. Moreover, chronic pain frequently coexists with psychological conditions like depression and anxiety, which further complicates treatment and underscores the need for a comprehensive therapeutic approach[1]. In addition, pharmacological interventions for chronic pain—particularly opioid analgesics—are frequently associated with significant adverse effects, raising concerns regarding their long-term safety and efficacy[33].

Types of chronic pain

The International Association for the Study of Pain (IASP) collaborated with the World Health Organization (WHO) to form a Task Force dedicated to the Classification of Chronic Pain. They define chronic pain as pain persisting or recurring for more than three months. Chronic primary pain refers to pain in one or more anatomical areas that cannot be attributed to another underlying condition, aimed at classifying a significant group of chronic pain cases with an unclear cause. Other forms of chronic pain are associated with specific primary conditions or identifiable insults, where pain is a symptom. These include chronic cancer-related pain, chronic postsurgical or post-traumatic pain, chronic neuropathic pain, chronic headache or orofacial pain, chronic visceral pain, and chronic musculoskeletal pain[31]. Correctly identifying the type of chronic pain in a patient is crucial, as varying etiologies and diagnoses necessitate distinct treatment approaches, and individual factors may further inform the optimal course of management.

CPGS

The Chronic Pain Grade Scale (CPGS) is a widely used tool for assessing the severity and impact of chronic pain[3]. It categorizes pain into different grades based on its intensity and the level of disability it causes in a person's daily life. The scale evaluates both the pain intensity and the degree to which pain interferes with usual activities, allowing for a comprehensive assessment of the functional limitations experienced by patients. The CPGS is particularly valuable in both clinical and research settings, as it helps to stratify patients according to the severity of their pain, guiding treatment decisions and enabling more targeted interventions[4]. Additionally, it can be used to monitor changes in pain and function over time, offering insights into the effectiveness of therapeutic strategies.

Ketamine - current state of knowledge

Ketamine Characteristics

Ketamine is a lipid-soluble compound with a dissociation constant close to the physiological pH.[7]. The molecule has a chiral center at the C2 position, giving rise to two optical isomers: S-ketamine and R-ketamine. In medical applications, both the racemic mixture and S-ketamine are available as hydrochloride salts, which are soluble in water[7]. The active enantiomer, S(+)-ketamine (with "S" indicating its spatial configuration and right-handed light rotation), is twice as potent as the racemic mixture and four times more potent than the R(−)-ketamine isomer. S(+)-Ketamine is marketed under the name Ketanest® in several European countries, including Germany, Austria and the Netherlands[8].

Ketamine Pharmacokinetics

Once absorbed into the body, ketamine quickly distributes to the brain and other highly perfused tissues. In humans, it has a short alpha half-life of 2 to 4 minutes and a longer beta half-life of 2 to 4 hours. The combination of a brief alpha half-life and a short context-sensitive half-time aligns with the rapid recovery typically observed following intravenous ketamine anesthesia[8]. Systemic clearance of ketamine ranges from 60 to 147 L/h for a 70 kg individual, a rate comparable to liver blood flow, which accounts for the drug's low oral bioavailability [10]. When S-ketamine is administered on its own, it shows a significantly higher systemic clearance compared to when it is part of a racemic mixture, indicating that R-ketamine may inhibit the clearance of S-ketamine [9]. In elderly patients or those with hepatic cirrhosis, a reduction in hepatic blood flow leads to reduced clearance of ketamine, thereby increasing its oral bioavailability [10]. The elimination half-life of S-ketamine is slightly longer, approximately 4 to 7 hours, than that of the racemic mixture.

Biotransformation and interactions

Ketamine is extensively metabolized through oxidation, primarily undergoing N-demethylation to produce metabolites such as norketamine, 4-hydroxy-ketamine, and 6-hydroxy-ketamine. Norketamine is the main metabolite found in humans and has pharmacological activity. It is further broken down into 6-hydroxynorketamine[11]. After undergoing glucuronidation, ketamine metabolites are eliminated through bile and urine, with only minimal amounts of the parent drug detectable in urine [8]. Both optical isomers of ketamine are demethylated at similar rates by human liver microsomes [12]. Additionally, R-ketamine is not produced following the intravenous administration of S-ketamine in humans, indicating there is no interconversion between the two isomers [13].

The N-demethylation of ketamine is reduced in vitro when cytochrome P450 enzymes, specifically CYP3A, CYP2B6, and CYP2C9, are inhibited[14].In vitro studies using human liver microsomes have shown that CYP2B6 is involved in the metabolism of ketamine [14]. This was later validated in vivo with healthy volunteers, where the metabolism of oral S-ketamine was reduced by the CYP2B6 inhibitor ticlopidine [13].

Mechanism of Action

Ketamine produces its analgesic, antidepressant, and psychomimetic effects through multiple pathways. Its main mechanism involves acting as a noncompetitive antagonist at the phencyclidine binding site of N-methyl-D-aspartate (NMDA) receptors in the central nervous system (CNS), especially within the prefrontal cortex and hippocampus. This action reduces both the frequency of NMDA channel opening and the duration the channels remain in an active, open state[15]. The NMDA receptor is a ligand-gated ion channel primarily activated by glutamate, the main excitatory neurotransmitter in the CNS. Inhibition of this receptor leads to reduced neuronal activity. The activation of NMDA receptors is crucial for various functions, including cognition, chronic pain modulation, opioid tolerance, and mood regulation. It is also considered the key receptor involved in the processes of central sensitization and windup[16].

Low- dose ketamine administration exerts ‘antihyperalgesic and antiallodynic’ effects via NMDA receptor antagonism. In higher doses, ketamine (full anesthetic doses) results in activation of different types of opioid receptors with various affinities (μ- , κ- , σ- opioids). However, the antinociceptive effects of ketamine are not reversed by naloxone, which suggests that its interactions with opioid receptors are not the primary source of analgesia[15]. Ketamine's diverse pharmacological effects may result from its interaction with multiple receptor systems. These include antagonistic actions on nicotinic and muscarinic acetylcholine receptors, inhibition of voltage-gated calcium channels, local anesthetic effects through sodium channel blockade, agonistic activity at high-affinity D2 dopamine receptors, and enhancement of γ-aminobutyric acid (GABAA) signaling[15]. Ketamine is available as a racemic mixture containing two stereoisomers: R(–)-ketamine and S(+)-ketamine. The S(+)-isomer is about 3–4 times more potent as an anesthetic than the R(–)-isomer due to its higher affinity for the phencyclidine (PCP) binding site on the NMDA receptor. Compared to the racemic form, S(+)-ketamine has a shorter duration of action, causes more drowsiness, and provides superior analgesic effects while producing fewer hallucinogenic side effects. In contrast, the R(–)-isomer acts as a stronger σ-agonist, which may contribute to the lowered seizure threshold associated with ketamine use[16]. Ketamine is unique among clinical drugs for its combination of hypnotic, analgesic, and amnestic effects. Its hypnotic effects may result from the inhibition of hyperpolarization-activated cyclic nucleotide-modulated (HCN1) cation channels, which are involved in stabilizing membrane potential and regulating spike frequency by mediating "sag" currents. The mechanisms behind ketamine's amnestic effects are not fully understood but are likely due to its interactions with multiple receptors, including NMDA, serotonin, and nicotinic acetylcholine receptors[18]. Ketamine is well-documented for its effectiveness at sub-anesthetic doses (less than 0.5 mg/kg) in alleviating postoperative pain. It reduces the need for opioid analgesics and lowers the incidence of nausea and vomiting, while maintaining manageable side effects[17].

Dosing and Administration Routes

Ketamine can be administered via various routes, including intravenous (IV), intramuscular (IM), oral, and intranasal. The IV route is most commonly used in chronic pain management, particularly for infusions. The dosing of ketamine varies depending on the condition being treated and the patient's response. Low-dose ketamine infusions have been shown to provide significant pain relief with a relatively low incidence of adverse effects[17,21]

Ketamine in Different Types of Chronic Pain

Neuropathic Pain

Neuropathic pain, resulting from nerve damage, is notoriously difficult to treat with conventional analgesics. Ketamine infusion has been shown to alleviate pain in numerous patients who have not responded to various other pharmacological and cognitive-behavioral treatments[22]. A recent trial investigated the effects of a single 0.5 mg/kg dose of ketamine in 20 patients with neuropathic pain from various causes, including surgery, radiculopathy, trauma, diabetes mellitus, or chemotherapy. The study found no significant relief of neuropathic pain at 5 weeks post-treatment (the primary outcome), although a modest effect was noted at 1 week (the secondary endpoint[23]. There are studies in animal that suggest ketamine has long-term anti-

allodynic effects when used over a prolonged period (more than 3 days) but does not produce similar effects after a single dose[24].Pain relief with IV ketamine has been observed as early as 48 hours after the infusion and may last for two weeks or longer, particularly with higher-dose regimens. While reductions in pain scores have been noted across various dosages, stronger analgesic effects were seen with higher doses[29]. Ketamine's ability to modulate central sensitization and its anti-inflammatory properties are thought to be key factors in its success in treating neuropathic pain.

Cancer-Related Pain

Cancer-related pain is a complex and multifactorial condition that often requires a multimodal approach to management. Ketamine has been investigated as an adjunct to opioid therapy in cancer patients, with studies reporting enhanced pain relief and reduced opioid requirements[19,20]. The NMDA receptor antagonism by ketamine is particularly beneficial in managing opioid-resistant pain, providing an alternative pathway for pain control[22]. Furthermore, ketamine's rapid onset of action makes it suitable for managing breakthrough pain in cancer patients.

Pain in Fibromyalgia and Other Pain Syndromes

Fibromyalgia and other chronic pain syndromes, such as complex regional pain syndrome (CRPS), are characterized by widespread pain and heightened pain sensitivity. Ketamine's ability to disrupt central sensitization processes has shown promise in these conditions. Clinical trials and case studies have reported significant pain relief in fibromyalgia patients following ketamine infusions.In patients with CRPS1 and those with small-fiber neuropathy, pain relief lasting more than 24 hours has been noted following a brief infusion of 0.5 mg/kg of S-ketamine.Comparable results have been observed in animal models of neuropathic pain[21]. Many studies indicate that the use of IV ketamine or S-ketamine during the perioperative period may reduce the risk of developing chronic postsurgical pain (CPSP) in patients undergoing surgery[30].

However, the variability in individual responses and the need for repeated treatments highlight the challenges in using ketamine for these syndromes.

Comparison with Other Treatments

Ketamine vs Opioids

Opioids have long been the cornerstone of chronic pain management, but their use is marred by the risks of addiction, tolerance, and side effects. Ketamine offers an alternative with a lower risk of dependency and a different mechanism of action, making it a valuable option for patients who are opioid-tolerant or seeking to reduce opioid use. Antihyperalgesic doses of ketamine have been shown to reduce central sensitization in both painful animal models and human volunteers exposed to various pain stimuli, as well as in the postoperative period. Numerous studies have demonstrated that ketamine's effects are achieved when administered as a perioperative bolus (0.1 to 0.5 mg/kg), followed by a continuous infusion (1 to 2 microg/kg per minute) during the perioperative period and extending for 48 to 72 hours post-anesthesia[26]. When used intravenously in combination with opioids, ketamine has the potential to manage pain in patients who require escalating doses of medication to control severe pain[27].

Ketamine vs Non-Pharmacological Therapies

Non-pharmacological therapies, such as physical therapy, cognitive-behavioral therapy (CBT), and acupuncture, are essential components of chronic pain management. While these therapies focus on improving function and coping strategies, ketamine directly targets pain pathways. There are findings in rats that show rats that didn’t respond with anti-allodynic effect to spinal cord stimulation, did respond with anti-allodynic effect on combination of spinal cord stimulation and sub-effective dose of ketamine i.t. Additionally, the duration of the anti-allodynic effect of spinal cord stimulation (SCS) was prolonged in both responders and non-responders when combined with an intrathecal (i.t.) sub-effective dose of ketamine[25].

Side effects of ketamine treatment

Ketamine, increasingly used in the treatment of chronic pain, is associated with several side effects that can limit its use. Literature highlights that the most common adverse effects are neuropsychiatric symptoms, such as hallucinations, disorientation, and euphoria. These side effects are primarily due to ketamine's

antagonism of NMDA receptors in the brain, leading to altered perception and cognition. The frequency and severity of these symptoms can vary depending on the dose and method of administration. In addition to its effects on the nervous system, ketamine can also cause cardiovascular side effects. Review articles point to the risk of elevated blood pressure and increased heart rate, which is particularly concerning for patients with pre-existing heart conditions. These hemodynamic effects are related to ketamine's sympathomimetic action, which can amplify the body's stress response. Another important aspect is the potential for nephrotoxicity and hepatotoxicity. Long-term use of ketamine, especially at high doses, has been linked to the risk of liver and kidney damage. Studies suggest that chronic exposure to ketamine can lead to bladder fibrosis and kidney failure, necessitating careful monitoring of patients undergoing prolonged therapy.

Limitations and Challenges

Despite its potential, the use of ketamine in chronic pain management is not without limitations. The variability in patient responses, the need for repeated treatments, and the potential for side effects necessitate careful patient selection and monitoring. The effectiveness and long-term safety of oral ketamine for chronic pain management are not well established, which limits its routine use. Some studies on oral ketamine have reported low success rates, often due to treatment failures or the occurrence of adverse effects. Its widespread clinical application is further restricted by psychotomimetic and other side effects. However, ketamine has shown analgesic benefits in patients with severe pain that has not responded to standard treatments. In such cases of intractable pain, oral ketamine might be beneficial. Therefore, it may have a limited role as an add-on therapy for managing complex chronic pain when other options have proven ineffective[28]. Additionally, the lack of standardized protocols for ketamine use in chronic pain highlights the need for further research to establish optimal dosing, administration routes, and long-term safety profiles. Further research is needed to identify the ideal patient population and conditions for this treatment, determine the optimal dosing regimen, assess whether combination therapy with ketamine is more beneficial than using it alone, and evaluate the impact on both physical and psychological functioning, as well as the long-term adverse effects.

Conclusions

Ketamine represents a promising option for the management of chronic pain, particularly in cases where traditional therapies have failed. Its unique mechanism of action, rapid onset of effect, and ability to enhance the efficacy of other treatments make it a valuable tool in the pain management arsenal. Ketamine, an NMDA receptor antagonist with additional activity on opioid receptors, has been investigated as a pharmacological treatment for chronic pain disorders. Randomized controlled trials (RCTs) have demonstrated that ketamine can be an effective therapeutic option for Complex Regional Pain Syndrome (CRPS) and Phantom Limb Pain (PLP), especially in cases that are resistant to conventional treatments. It is also recommended for refractory mixed neuropathic pain. Moreover, ketamine has shown promise as a long-term pharmacological intervention for depression, which frequently coexists with chronic pain and may influence its progression. However, its analgesic benefits must be weighed against potential adverse effects, including psychomimetic and dissociative symptoms. While clinical evidence remains inconclusive, there is also emerging potential for ketamine to reduce opioid consumption, both through its direct analgesic properties and its ability to mitigate opioid-induced hyperalgesia. Despite these findings, research on ketamine for chronic pain management is still limited, with a notable scarcity of high-quality RCTs assessing its efficacy in various pain conditions. Furthermore, several of these studies suffered from limitations such as insufficient blinding, small sample sizes, limited statistical power, and short follow-up durations. Nevertheless, given that ketamine is relatively inexpensive and widely accessible compared to other pharmacological treatments for chronic refractory pain, it is probable that future research will continue to explore its efficacy, as well as the most effective dosing and administration strategies.

Disclosures:

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Writing - review and editing: Dawid Sewruk and Karol Kanon
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