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KETAMINE IN PAIN MANAGEMENT AND PSYCHIATRIC TREATMENT: CURRENT KNOWLEDGE AND IMPLICATIONS FOR CLINICAL PRACTICE

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ABSTRACT

Research objectives: Ketamine, a derivative of phencyclidine, is a dissociative anesthetic that is used not only in anesthesia but also in analgesic and psychiatric settings such as perioperative and chronic pain, opioid-induced hyperalgesia and treatment-resistant depression management. With the general population's prevalence of 2-40% for chronic pain and similar lifetime values for depression, ketamine deserves attention as an alternative to commonly used treatments. This research describes the use of subanesthetic (0,3 mg/kg to 0,5 mg/kg) ketamine doses in pain management and psychiatric settings, discusses its safety concerning psychomimetic and physical adverse effects and dependence risk, and suggests future research directions.
Methods: Review of literature including peer-reviewed studies, meta-analyses, randomized controlled trials, clinical guidelines, focusing on ketamine pharmacokinetics, anesthetic and antidepressant effects, safety and clinical applications.
Findings: Ketamine produces satisfactory short-term pain alleviation and rapid antidepressant action. It is part of multimodal anesthesia protocols as an adjuvant to other local anesthetics, prolonging their effects, and is a safe alternative for analgesia in opioid-tolerant patients. It has many routes of administration, which is used in patients with difficult intravenous access in emergencies. It provides a beneficial respiratory effect, alleviates chronic neuropathic and cancer pain, offers rapid response in acute depression including suicidal ideation, prevents post-operative depression risk and supports neuroplasticity.
Conclusions: Ketamine is a promising drug in anesthesiology and psychiatry, but its long-term safety is not yet determined. Future research should focus on identifying biomarkers that determine treatment response, optimizing dosage, and discovering safer derivatives.

KEYWORDS

Chronic Pain, Esketamine, Ketamine, Neuroplasticity, Opioid-Induced Hyperalgesia, Treatment-Resistant Depression

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Introduction

Ketamine was synthesized as an alternative to phencyclidine, with fewer adverse effects than the original drug - having lesser hallucinatory potential and being a shorter-acting agent. Ketamine, commonly defined as a "dissociative anesthetic", acquired this label due to the patient's feeling of disconnection from the environment with a concomitant sensation of floating in outer space and loss of sensory input from the limbs (Hirota & Lambert, 2022). Soon, ketamine was found to produce analgesic effects (Richards et al., 2025) with a beneficial hemodynamic profile preserving blood pressure (Riccardi et al., 2023), letting it find its place in the arsenal of general anesthesia drugs. Repeated studies confirmed ketamine's potential in reducing opioid use in perioperative care (Peltoniemi et al., 2016; Riccardi et al., 2023; Richards et al., 2025).

Ketamine is used in a wide array of settings, ranging from the operating room (Richards et al., 2025), intensive care units (Patanwala et al., 2017) and Emergency Department (Ying & Zuo, 2023), to psychiatric use cases like treatment-resistant depression (TRD) management (Kim et al., 2024), anxiety disorders such as obsessive-compulsive disorder (OCD), along with substance use disorders (SUD) (Martinotti et al., 2021) and suicidal ideation with intent (Ionescu et al., 2020).

Incidence of chronic pain is common in the general population, ranging from 2 to 40%, frequently coinciding with mental health diseases (depression, anxiety, substance abuse and suicide), suggesting shared underlying mechanisms behind these conditions. Such overlap is clinically meaningful: individuals with chronic pain are more likely to develop mood disorders, while psychiatric symptoms can exacerbate pain perception and functional impairment (Hooten, 2016). Moreover, chronic pain may be aggravated by long-term opioid therapy, leading to the development of opioid-induced hyperalgesia (OIH). Reducing the risk of hyperalgesia and subsequent chronic pain requires limiting the use of opioids in the perioperative care (Barrett et al., 2020; Dagher et al., 2025). However, even though clinical guidelines recommend cautious opioid use

for chronic non-cancer pain, opioids are still the most frequently prescribed drug group for chronic pain (Coffee et al., 2024). At the same time, with the fourth wave of the opioid crisis in the US, the escalation of illicit fentanyl and fentanyl analogues overdose-related deaths and polysubstance abuse (Ciccarone, 2021), there is a growing need to find alternatives in the field of acute and chronic pain management (Garland, 2014; Pourmand et al., 2017) that stimulates the interest in multimodal analgesia and opioid-free anesthesia. In these approaches, ketamine plays an important role due to its efficacy in reducing peri-operative opioid intake (Peltoniemi et al., 2016; Riccardi et al., 2023; Richards et al., 2025), beneficial respiratory effect (Barrett et al., 2020), as well as a useful analgesic in patients with preoperative opioid use (Meyer-Frießem et al., 2022).

Importantly, ketamine's dual potential in analgesia and mood regulation brings up the necessity for interdisciplinary cooperation and discussion between specialists regarding a common consensus not only on treatment schemes for patients requiring complex care but also for potential risks of prolonged ketamine use, including increased tolerance or substance dependency; along with far more dangerous health hazards like memory loss or cystitis (Morgan et al., 2012). What ketamine offers in this instance is its previously described spectrum of effects, including pain management, mood regulation, its role as an anesthetic, and also the impact on neuroplasticity (M. Wu et al., 2021), which seems interesting from a multidisciplinary point of view.

This evidence-informed narrative review aims to summarize the pharmacological mechanisms of action, both in psychiatric conditions and pain management, reviews its applications in acute and chronic pain, examines the evidence for ketamine use in depression treatment and highlights not only the potential, but also the dangers of misuse. We also aimed to provide conclusions for clinical practice in anesthesiology and psychiatry, discussing the integrated perspective and the need for standardized protocols.

Pharmacology of ketamine

Ketamine is a racemic mixture of two enantiomers: R-ketamine and S-ketamine, in equal amounts (Hashimoto, 2019). The main mechanism of action concentrates on antagonising the N-methyl-D-aspartate (NMDA) receptor, resulting in analgesic and anesthetic effects (Anis et al., 1983) along with antidepressant and amnesic effects (Zanos et al., 2018), not to mention the sensory perception alteration (Oye et al., 1992). NMDA receptors operate on glutamate transmission, standing for primary excitatory neurotransmission in the human brain, also associated with synaptic plasticity, which is believed to play a significant role in memory formation (Jewett & Thapa, 2025).

Another important part of glutaminergic transmission occurs through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors also responsible for synaptic plasticity, interestingly shown to be depleted in amounts in a process called long-term depression. Fortunately enough, glutaminergic stimulation, acting through long-term potentiation with AMPA receptors, may cause the insertion of those receptors back into the synaptic surface (de León-López et al., 2025). Worth mentioning would also be the reports of ketamine's impact on dopamine transmission (H. Wu et al., 2021), involved not only in motivation and pleasure but also in pain perception (Taylor et al., 2016). Beyond dopaminergic influence, serotonin impact adds to analgesic and antidepressant attributes of ketamine. Due to binding to the 5-HT1b receptor, ketamine helped alleviate major depressive disorder in this study (Tiger et al., 2020). From a psychiatric point of view ketamine has been discussed as a rapid acting antidepressant (RAAD) with its mechanism of action resulting in fast changes in synaptic function and plasticity through increased mammalian target of rapamycin complex 1 (mTORC1) signalling (thanks to glutamate transmission and AMPA receptor activation) resulting in the increased amount of neuron connections between prefrontal cortex (PFC) and other structures of the limbic system (Duman et al., 2016) which is responsible not only for cognitive and emotional regulation but also visceral and autonomic balance (Torrico & Abdijadid, 2025).

Notably, ketamine's pharmacological effect is not limited to this, as it has been observed that ketamine impacts other receptors and ion channels, such as opioid and cholinergic receptors, as well as hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. HCN channel antagonism is shown to complement the anesthetic effect of NMDA receptor inhibition, together with antidepressant properties mediated through the mTOR pathway and attenuation of pain hypersensitivity. Although the analgesic effects of ketamine seem to be caused primarily by NMDA blockade, ketamine binds to mu opioid receptors, as well as kappa and delta receptors with lower affinity (Subramanian et al., 2022). Interestingly, there has been a decline in the antidepressant properties of ketamine with co-administration of naltrexone, suggesting the opioid system's role in the mood-stabilizing impact of ketamine (Williams et al., 2018).

Research indicates that S-ketamine is about 4 times more effective than R-ketamine when it comes to pain perception reduction; however, it is also more prone to cause audiovisual disturbances (hallucinations)

(Oye et al., 1992). Additionally, S-ketamine is described as being 2 times more potent in anesthesia induction (Zanos et al., 2018) along with more rapid recovery of psychomotor skills than the racemic mixture of ketamine enantiomers (White et al., 1985). Consequently, R-ketamine appears to have a more potent antidepressant effect than S-ketamine, which is consistent with the antidepressant profile of ketamine's metabolites (2R,6R)-HNK (2R,6R-hydroxynorketamine) exhibiting higher antidepressant potential than (2S,6S)-HNK (2S,6S-hydroxynorketamine) (Zanos et al., 2018). Ketamine is metabolised to norketamine (with major participation of CYP2B6 and CYP3A4), which is then further metabolised (by CYP2A6 and CYP2B6) to hydroxynorketamines (HNK) and dehydronorketamines (DNK) (Hess et al., 2022). Norketamine appears to exert a residual anesthetic effect, while HNK metabolites have been shown to have antidepressant qualities without concomitant anesthesia (Zanos et al., 2018). Intravenous administration of 1-2 mg/kg of racemic ketamine elicits an immediate anesthetic effect (after 1-2 minutes), while 1-6 mg/kg/h is required to maintain this effect (Kohtala, 2021). According to Zanos (Zanos et al., 2018), awakening from anesthesia involving ketamine occurs 11 minutes post-administration. Ketamine may also be administered intramuscularly, orally, intranasally, by inhalation, as well as rectally (Peltoniemi et al., 2016) however, bioavailability and action onset significantly vary. Intramuscular route is characterised by the highest bioavailability (93%) and starts to exert its effects after 5 minutes (Clements et al., 1982) making it a valuable option when sedating patients with difficult intravenous access. As an alternative method in an emergency setting, nebulization or intranasal administration of ketamine could also be considered, with its bioavailability ranging from 20 to 40% (Cetin et al., 2025) and 45-50% respectively (Zanos et al., 2018). Oral bioavailability is limited to 16-29%, due to extensive first-pass hepatic metabolism, with Cmax values after 40-55 minutes after ingestion. The sublingual route allows for 24-30% availability with a shorter time to reach Cmax than for oral administration. Rectal administration accounts for a similar bioavailability to the sublingual route, making it a subject for consideration if other routes of administration are unfeasible (Peltoniemi et al., 2016). What is also worth mentioning is the fact that due to ketamine's elimination half-life (2-4h), upon infusion, there may be a need to titrate down on the dosage (Hill, 2004).

Sympathomimetic action of ketamine is exerted through endogenous catecholamine release, vagal inhibition and reduction of catecholamine reuptake (Peltoniemi et al., 2016; Riccardi et al., 2023; Richards et al., 2025). Direct negative inotropic effect on the heart, which is balanced by the aforementioned catecholamine release, highlights its complex effects on the cardiovascular system. Increased myocardial oxygen demand contributes to increased coronary perfusion (Richards et al., 2025).

Pain

Acute perioperative pain

As discussed earlier, ketamine's analgesic qualities in subanesthetic doses might be of importance in the treatment of acute pain, especially in emergency settings or in opioid-tolerant patients. So-called low-dose of ketamine, if administered perioperatively, be it in a form of 10-minute infusion, or a bolus, is defined as the dose <1,2mg/kg/h or 1 mg/kg intravenous bolus. Such a dose not only reduces post-operative pain and has an opioid-sparing effect but also reduces nausea and vomiting (Peltoniemi et al., 2016). Commonly used ketamine doses to account for sufficient analgesia range from 0,3 mg/kg to 0,5 mg/kg in bolus form, followed by infusion of 0,1-0,2 mg/kg/h (Schwenk et al., 2018).

Associated with prolonged opioid use, NMDA receptor activation in the posterior horn sensory neurons is a primary mechanism for opioid-induced hyperalgesia, which puts patients at risk of developing chronic post-operative pain. Activation of NMDA receptors causes wind-up response, reducing the pain threshold and causing central sensitisation (Zhang et al., 2025). Ketamine, as a non-competitive NMDA antagonist, disrupts this process, leading to alleviation of OIH symptoms (Riccardi et al., 2023), thus reducing the need for opioids (opioid-sparing effect) and exhibiting a beneficial influence on peri-operative nausea and vomiting (Peltoniemi et al., 2016). Prolonged post-operative pain incidence reaching 50% (Riccardi et al., 2023), might be the rationale for the use of ketamine in this setting.

On the other hand, several recent studies are comparing acute pain management with an opioid and ketamine, which show inconclusive results. In the meta-analysis by Guo et al. (Guo et al., 2024), there has been a discrepancy between the early and late effects of morphine vs ketamine, where ketamine was proven more efficient in decreasing numeric rating scale (NRS) scores in the ketamine-treated group at 15 and 30 minutes. However, after 120 minutes, the morphine group had lower NRS scores. This finding suggests a different analgesic profile of ketamine, which might complement traditional pain management strategies.

Ketamine is also extensively incorporated in the multimodal anesthesia protocols, next to simple analgesics like acetaminophen or regional blockades. It has even been used as an adjuvant to a local anesthetic in regional anesthesia, where it was able to prolong the analgesic effect by 3 hours, and in peripheral nerve block up to 6 hours (Xiang et al., 2024). Moreover, co-administration of magnesium intraoperatively allows for morphine consumption reduction by nearly 50% (Varas et al., 2020). Owing to ketamine's antidepressant properties, it influences the incidence of post-operative depression, and its effect persists for longer than a month (Bi et al., 2021).

Another advantage of ketamine, especially useful in patients with obstructive sleep apnea (OSA) or obesity, is its ability to maintain airway patency, in contrast to opioids that cause dose-dependent respiratory depression, diminishing the ventilatory drive. General anesthesia enhances this issue even more, promoting airway obstruction in these patients. Ketamine, however, especially in low doses, acting as a bronchodilator and displaying a minimal impact on the central respiratory response, might be applicable in this scenario (Carron et al., 2024). Notable influence of ketamine on the bronchial tree in the form of bronchorrhea (Richards et al., 2025) as well as the tendency for hypersalivation rarely is the source of complications, especially after co-administration of atropine (Heinz et al., 2006).

Ketamine owes its resurgence in trauma, prehospital acute pain management and its role in induction for procedural sedation, to its early onset of action (Chou et al., 2025) and a possibility for use in patients with hypotension, preserving the blood pressure (Richards et al., 2025). Ketamine has been proven in a meta-analysis by Ying and Zuo (Ying & Zuo, 2023) to cause a significant decline in pain scores after 30 minutes, compared to any control group. An optimal dose of 0,3 mg/kg has been obtained in this study. Despite ketamine's benefits, the study also observed a significant difference in the neurological side effects, such as dizziness, dysphoria and emergence phenomenon, between the ketamine and placebo/morphine groups.

Chronic pain

Promising indications for ketamine in chronic pain management point towards Complex Regional Pain Syndrome (CRPS) and neuropathic pain. CRPS may develop after surgeries on extremities, trauma or fractures (but in some cases etiology remains unclear) and is characterized by debilitating pain of neuropathic nature, hyperalgesia and autonomic dysfunction (Shekarsarai et al., 2025). There are 2 variations of CRPS, where type 1 is linked to an identifiable nerve lesion that could not be found in type 2 (Marinus et al., 2011). Ketamine showed short-term statistically significant effects in this disease entity, especially administered intravenously, according to several studies (Fassio et al., 2022; Shekarsarai et al., 2025); however, making careful monitoring indispensable (Shekarsarai et al., 2025). Topical ketamine has also been studied in patients with CRPS, where it didn't lead to significant pain reduction; however, it has relieved allodynia (Finch et al., 2009). There are also many ongoing trials in this field (Tékus et al., 2025). Similarly, in fibromyalgia, ketamine allowed for short-term symptom relief, while the long-term effect remained unsatisfactory (de Carvalho & de Sena, 2024).

Meta-analysis by Guimarães Pereira et al. (Guimarães Pereira et al., 2022) stated that ketamine remarkably (28-46%) decreased neuropathic pain compared to the control group, with effects lasting up to 2 months after the end of the treatment. Of note, the incidence of psychomimetic adverse effects increased in the ketamine group. Regarding cancer pain, especially of a neuropathic nature, ketamine is also considered a helpful addition to the pain management strategy. Apart from infusions, oral and intranasal administration is studied as well, with favourable results (Culp et al., 2020). 65% of patients experiencing breakthrough cancer pain achieved a 40% NPIS (Numerical Pain Intensity Scale) score decline from baseline levels in the intranasal ketamine group, compared to a 20% decline in the placebo group (Carr et al., 2004). Interestingly, in a meta-analysis by Jiao et al., the most pronounced pain reduction has been observed in PCEA (Patient-controlled epidural analgesia), compared to PCSA (patient-controlled subcutaneous analgesia) and PCIA (patient-controlled intravenous analgesia) (Jiao et al., 2024). According to the American Society of Pain and Neuroscience (ASPN), ketamine should be considered individually for each patient, for refractory neuropathic, bone and mucositis-related pain (Aman et al., 2021). Importantly, the anti-depressive effect provided by ketamine might contribute to overall pain reduction in these patients. Since patients with cancer pain have also markedly elevated (3,5-fold) the risk of depression, ketamine's combined analgesic and mood-modulating properties may encourage this choice of antidepressant (Jiao et al., 2024).

Considering the applicability of ketamine in migraine management, studies show inconclusive results (Schwenk et al., 2021; Yuan et al., 2023). Meta-analysis by Chah et al. (Chah et al., 2021) shows non-superiority of ketamine in comparison to placebo, prochlorperazine and diphenhydramine; however, it might positively impact the severity of aura.

Ketamine uses in psychiatry

Although ketamine has been commonly used in anesthetics for over half a century, it wasn't widely recognised as a psychiatric drug until 2019 when the United States Food and Drug Administration approved the use of S-ketamine hydrochloride in the form of a nasal spray (SPRAVATO™) for treatment-resistant depression (TRD) (*Drug Approval Package*, n.d.). However, one of the first times an antidepressant effect of this substance was described dates to the year 2000, when a placebo-controlled double-blind trial involving intravenous administration of either ketamine hydrochloride in sub-anesthetic dose or saline solution in patients diagnosed with major depression was conducted. It concluded that NMDA receptor antagonists may have a potential effect on depression treatment (Berman et al., 2000) as an addition to the previously recognised monoaminergic hypothesis (Hirschfeld, 2000).

Depression is a mental condition and a global health issue affecting one in ten adults at some point in their lives, although indications of even higher lifetime prevalence (30-40%) can be found (Herrman et al., 2022). In their systematic review of worldwide studies, Haroz et al. specify depression symptoms to be: sadness, loss of energy, problems with sleep, social isolation, problems with appetite and/or weight, increased amounts of crying, loss of interest, general aches and pains, suicidal thoughts and anger (Haroz et al., 2017). Treatment focuses on psychotherapeutic and pharmacological actions (Herrman et al., 2022), which, although crucial and to a great extent effective, unfortunately require at least a few weeks for their results to be noticed, sadly leaving about a third of patients still in need for further interventions, bringing us to a term of treatment-resistant depression - a situation with no response to treatment using two or more classical antidepressants (Kim et al., 2024). This is a moment to consider implementing ketamine as a rapid-acting antidepressant (RAAD) into treatment, and several studies confirm its positive outcome - ketamine being administered either intravenously or intranasally. That being said, a study by Singh et al. concluded that a 40-minute intravenous infusion of at least 0.2 mg/kg of S-ketamine resulted in rapid (within 2 hours) and robust antidepressant effect (Singh et al., 2016) and another study by Daly et al. concluded that a dose of at least 28mg of intranasal S-ketamine provided a significant decrease in depressive symptoms with an even more persistent effect of 56 and 84mg intranasal doses (corresponding to 0.2mg/kg and 0.5mg/kg intravenous doses respectively) administered twice or once weekly, lasting up to 2 months after cessation of S-ketamine use (Daly et al., 2018).

Although psychiatry, contrary to other medical fields, to a relatively great extent bases diagnostic processes and treatment actions on subjective assessment of symptoms that patients experience, with no laboratory parameters that would specifically indicate treatment success or failure, there are radiological findings supporting theoretical approaches. In their meta-analysis of studies on structural brain abnormalities (visualised via magnetic resonance imaging) in patients diagnosed with major depressive disorder (MDD) in comparison to healthy subjects, Koolschijn et. al found brain volume reductions in frontal areas of the brain, along with PFC and hippocampal reductions - brain regions responsible for emotional processing (Koolschijn et al., 2009). Other studies also point out the correlation between reduced brain volume in those regions and the prevalence for further depressive episodes, some more severe or even treatment resistant (Belleau et al., 2019; Treadway et al., 2015). This brings up a term of neuroplasticity - the ability of the brain tissue to adjust to current needs such as increasing the amounts of neuronal synaptic linkage or neurons themselves and ketamine is a substance that seems to propagate those processes through aforementioned glutamatergic transmission and NMDA receptors, but also through AMPA receptors that further leads to brain derived neurotrophic factor (BDNF) release and mTOR phosphorylation. As a result of those actions increased number and function of synapses in the PFC can be expected with the reversal of their loss due to stress, which proves the antidepressant mechanism of action of ketamine (Li et al., 2010; Price & Duman, 2020; Zawilska & Zwierzyńska, 2024).

Safety

Thanks to ongoing research on ketamine's multipurpose use and its benefits in various medical situations, it is necessary to discuss short- and long-term effects and safety of continuous and repeated ketamine administration. This drug, just like opioid analgesics, is a strictly controlled substance with a potential for abuse and for many years has been used recreationally, most often in a crystal or powder form, administered intranasally (Marongiu et al., 2025) leading to various adverse effects. When it comes to recreational use and ketamine's acute toxicity, the main adverse effect occurring after a relatively high dose of ketamine intake would be a dissociative, schizophrenia-like state involving unrealistic, even near-death perceptions, commonly known as a K-hole. Administration of a lower ketamine dose, on the other hand, results in a less harsh dissociative state with distorted time and space perception, accompanied by vivid hallucinations (Niesters et

al., 2014). A similar state has been described when waking up from ketamine-assisted anesthesia - emergence reactions varied from vivid illusions or floating sensations to outright delirium. Provided that the patient is also premedicated with midazolam (0,07-0,1 mg/kg), diazepam or lorazepam, the risk of emergence phenomenon is minimal. The incidence of this reaction is also attenuated when ketamine is co-administered with other sedative hypnotics (Pai & Heining, 2007). Ketamine has even been observed to reactivate psychosis in schizophrenia patients. Reports from Emergency Departments on patients admitted after ketamine use point out complaints like chest pain, anxiety, palpitations, confusion and memory loss and findings such as tachycardia, hypertension and slurred speech, some of these lasting up to 5 hours (Niesters et al., 2014; Weiner et al., 2000); however, ketamine may not have been the only substance in such patients' systems. There is a need for more studies with repeated ketamine infusion design to assess the safety profile more thoroughly. In prolonged ketamine intake, hence associated with its chronic toxicity, lower urinary tract symptoms like dysuria, smaller urine volume during more frequent micturition, hematuria, and lower abdominal pain (Kalsi et al., 2011) have been reported, which were attributed to ketamine-induced ulcerative cystitis (Niesters et al., 2014). The treatment of cystitis according to the majority of authors involves ketamine abstinence and initial oral treatment with NSAIDs, anticholinergics, antibiotics or steroids, escalating the treatment in intractable cases to intravesical or surgical management (Chan et al., 2022). Additionally, gastrointestinal complaints known as K-cramps, standing for vague abdominal pain, are attributed to biliary tract abnormalities (Beerten et al., 2023; Kalsi et al., 2011). Another alarming consequence of long-term ketamine use, and possibly the most important one for this research, is the development of tolerance and dependency on this substance. Tolerance can be described as a need for increased dose of substance to achieve the same effect (Kalsi et al., 2011) bringing up a risk of eventual neurotoxicity and dependence is defined in World Health Organisation's ICD-10 as 'cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state' (*ICD-10 Version:2019*, n.d.).

While the description of adverse effects caused by ketamine provided above refers to recreational ketamine use, it's worth remembering that ketamine is considered difficult to overdose, especially in clinical settings. Ketamine's lethal dose LD50 is more than 100x greater than its effective dose ED50 (Richards et al., 2025). It might, however, pose a risk of cardiac adverse effects, connected to its sympathomimetic activity. Even though ketamine generally elevates blood pressure and heart rate, in patients with heart failure, it might decrease contractility and sympathetic stimulation of the heart 4. Rise in BP and HR might be detrimental to patients with severe coronary artery disease or stenosis, especially with concomitant arterial hypertension. These factors might put the patient with a preexisting ischemic heart condition at risk of myocardial infarction or stroke. Therefore, ketamine should be avoided in certain patient groups - with SBP>180 mmHg, DBP>100 mmHg and unstable heart disease (Reede et al., 2023). Careful hemodynamic monitoring is required during continuous infusion of ketamine (Aman et al., 2021). Among cardiovascular effects, ketamine increases pulmonary artery pressure. It is controversial whether ketamine raises intracranial pressure, although it might increase cerebral blood flow, especially in patients with uncontrolled ventilation (Richards et al., 2025).

Discussion

This review highlights ketamine's unique pharmacological profile, positioning it as a multifaceted drug, combining hypnotic, analgesic and mood-stabilizing effects, acting through many different systems and receptors. Evidence demonstrates its consistent opioid-sparing properties, making it especially useful in OIH prevention and perioperative analgesia in opioid-tolerant patients. In the area of chronic pain as well as in TRD treatment, short-term benefits have been reported most consistently across research. Even though ketamine's adverse effects burden remains a concern, especially in the psychomimetic domain, when compared to opioids' risk of respiratory depression, OIH, nausea and vomiting, as well as tolerance and dependence, ketamine might provide a safer alternative or addition to existing protocols.

While most peri-operative trials demonstrate opioid-sparing effect and analgesic benefits of ketamine and S-ketamine with little to no adverse effects (Abu-Hussein et al., 2025; Hannon et al., 2023; He et al., 2025), the position of this drug in chronic pain management remains ambiguous.

Another clinically relevant characteristic of ketamine is its impact on inflammatory pathways - germane to the pathophysiology of both depression and chronic pain. Multiple inflammatory indicators have been associated with depression, one of them is the hypothalamic-pituitary-adrenal axis (HPA) hyperactivity, represented by elevated cortisol and CRP levels (Iob et al., 2020). This study also revealed that even though

inflammatory markers are correlated with cognitive-affective symptoms, the connection between inflammation and somatic symptoms is even more prominent (Iob et al., 2020). Ketamine as a therapeutic option has been explored in this study (Kiraly et al., 2017) considering its effect on immunity, where ketamine showed that IL-6 and IL-1a decreased in treatment-resistant depression patients 4h post-infusion, however, not correlating directly with a therapeutic effect.

When it comes to ketamine use in psychiatric practice, it is a relatively new therapeutic method, and although still in need of further research in terms of long-term effects of prolonged and repeated use, it also provides a direction for exploration of different mechanisms of depression in terms of neurotransmission and neuroplasticity, the latter also possibly contributing to pain management strategies. The problem with ketamine treatment in depression and suicidal ideation, though, seems to be its accessibility, as properly qualified specialists with access to certain equipment (intravenous infusion set, vital signs monitor, emergency kit) and a dedicated space for the procedure are required to ensure the safety of its intravenous administration, and the treatment itself is expensive unless refunded. Intranasal S-ketamine spray, on the other hand, although easier to administer, poses a threat of misuse if left to unattended utilization.

Existing consensus on the use of intravenous ketamine in acute pain management involves the following contraindications to ketamine use: severe cardiovascular disease (such as unstable angina, high-risk coronary vascular disease or poorly controlled hypertension), elevated intracranial/intraocular pressure, moderate or severe hepatic dysfunction, psychosis and pregnancy (Schwenk et al., 2018). Other contraindications when administering infusions for chronic pain include the following disease entities: hyperthyroidism, pheochromocytoma, full stomach aspiration risk, risk of intoxication or active substance abuse, delirium and refusal/inability to consent, added to the contraindications mentioned for acute pain (Cohen et al., 2018). The strongest indication evidence (grade B) exists for CRPS, where there is moderate evidence to support improvement for up to 12 weeks (Cohen et al., 2018). Lower quality evidence (grade C) recommends ketamine infusions for spinal cord injury pain. Similar to those already stated above, aneurysmal vascular disease or arteriovenous malformation, previous intracerebral hemorrhage and hypersensitivity to S-ketamine or ketamine are the contradictions for SPRAVATO™ use (*Drug Approval Package*, n.d.).

Evidence supporting ketamine's multimodal utility is constrained by methodological limitations, different dosing protocols, routes of administration, and sample size, resulting in difficulties in comparability. Long-term safety data, especially regarding repeated infusions, remains scarce, producing an uncertain risk of dependence or use outside of medical settings.

Conclusions and future directions

Thanks to ketamine's multimodal properties and its wide spectrum of action, this drug deserves multidisciplinary attention; however, it should require cautious and protocol-driven use due to its incompletely defined long-term role and safety profile. This research focuses on using subanesthetic ketamine doses in pain management and psychiatric conditions that offer effective analgesia in emergency settings, along with chronic pain alleviation and a rapid antidepressant response when previously prescribed treatment has failed.

Ketamine works through glutaminergic transmission, incorporating NMDA and AMPA receptors along with opioid, monoaminergic and HCN channels, all together responsible for its analgesic and antidepressant effects, but also dissociative ones. Although it should be used with utmost caution, possibly being harmful in patients with unstable cardiac disease or uncontrolled hypertension, thanks to its sympathomimetic cardiovascular profile, preservation of airway reflexes and bronchodilation, it's beneficial in specific anesthetic and emergency situations, when use of other available drugs could not be considered.

This substance provides a reliable reduction of perioperative opioid doses, helps to manage opioid-induced hyperalgesia, especially in high-risk or opioid-tolerant surgical patients and can even be attractive as a post-operative depression prevention, but when it comes to chronic use, data show mainly short-term pain management with some psychomimetic side effects.

Ketamine (especially one of its enantiomers - S-ketamine) offers a rapid, within a couple of hours, improvement in symptoms in TRD and suicidal ideation with its effect lasting up to several weeks and has been shown to provide neuroplastic changes in PFC and other limbic structures that are responsible for emotional processing and mood control, but its long term outcomes are still under investigation along with optimal dosing schedules and maintenance strategies.

The findings stress the need to further examine ketamine's prolonged use side effects, both physical and psychological, that could include cognitive disturbances, psychomimetic reactions and ulcerative cystitis, especially in high-dose exposure. Additionally, there's always a threat of tolerance and dependency

development, coming either from poorly controlled use or deliberate misuse, as ketamine has been used recreationally for years. Fortunately, this substance is generally considered safe in short-term clinical settings and hard to overdose lethally, but there is a need for strict misuse control, clear prescription criteria and limitations and long perspective research on repeated chronic medical use.

Overall, ketamine should be viewed through an interdisciplinary lens linking pain, mood and neuroplasticity, not as a routinely prescribed drug, but more as an individualised and guideline-based intervention with cautious patient selection basing on standardised protocols and with careful long-term monitoring to find the balance between its short-term benefits and uncertain long-term side effects, possibly ruling out the risk of addiction. In regard to future research directions, it seems necessary to focus on finding biomarkers indicating the prediction for response to the ketamine treatment, as well as integration for such interventions with nonpharmacological actions, further research on ketamine derivatives and their effects on symptom alleviation and also possible use in other medical conditions.

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REFERENCES

1. Abu-Hussein, B., Elrosasy, A., Samy, H., Ali, A. S., Alijla, S. S., Bitar, A. N., & Gamal, I. (2025). Efficacy and safety of S-ketamine in pain management for breast cancer patients undergoing modified radical mastectomy: A meta-analysis of randomized controlled trials. *Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*, *27*(8), 3325–3339. https://doi.org/10.1007/s12094-025-03847-8
2. Aman, M. M., Mahmoud, A., Deer, T., Sayed, D., Hagedorn, J. M., Brogan, S. E., Singh, V., Gulati, A., Strand, N., Weisbein, J., Goree, J. H., Xing, F., Valimahomed, A., Pak, D. J., El Helou, A., Ghosh, P., Shah, K., Patel, V., Escobar, A., … Narang, S. (2021). The American Society of Pain and Neuroscience (ASPN) Best Practices and Guidelines for the Interventional Management of Cancer-Associated Pain. *Journal of Pain Research*, *14*, 2139–2164. https://doi.org/10.2147/JPR.S315585
3. Anis, N. A., Berry, S. C., Burton, N. R., & Lodge, D. (1983). The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *British Journal of Pharmacology*, *79*(2), 565–575. https://doi.org/10.1111/j.1476-5381.1983.tb11031.x
4. Barrett, W., Buxhoeveden, M., & Dhillon, S. (2020). Ketamine: A versatile tool for anesthesia and analgesia. *Current Opinion in Anaesthesiology*, *33*(5), 633–638. https://doi.org/10.1097/ACO.0000000000000916
5. Beerten, S. G., Matheï, C., & Aertgeerts, B. (2023). Ketamine misuse: An update for primary care. *British Journal of General Practice*, *73*(727), 87–89. https://doi.org/10.3399/bjgp23X731997
6. Belleau, E. L., Treadway, M. T., & Pizzagalli, D. A. (2019). The Impact of Stress and Major Depressive Disorder on Hippocampal and Medial Prefrontal Cortex Morphology. *Biological Psychiatry*, *85*(6), 443–453. https://doi.org/10.1016/j.biopsych.2018.09.031
7. Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry*, *47*(4), 351–354. https://doi.org/10.1016/S0006-3223(99)00230-9

8. Bi, Y., Ye, Y., Zhu, Y., Ma, J., Zhang, X., & Liu, B. (2021). The Effect of Ketamine on Acute and Chronic Wound Pain in Patients Undergoing Breast Surgery: A Meta-Analysis and Systematic Review. *Pain Practice: The Official Journal of World Institute of Pain*, *21*(3), 316–332. https://doi.org/10.1111/papr.12961
9. Carr, D. B., Goudas, L. C., Denman, W. T., Brookoff, D., Staats, P. S., Brennen, L., Green, G., Albin, R., Hamilton, D., Rogers, M. C., Firestone, L., Lavin, P. T., & Mermelstein, F. (2004). Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: A randomized, double-blind, placebo-controlled, crossover study. *Pain*, *108*(1–2), 17–27. https://doi.org/10.1016/j.pain.2003.07.001
10. Carron, M., Tamburini, E., Linassi, F., Pettenuzzo, T., Boscolo, A., & Navalesi, P. (2024). Efficacy of nonopioid analgesics and adjuvants in multimodal analgesia for reducing postoperative opioid consumption and complications in obesity: A systematic review and network meta-analysis. *British Journal of Anaesthesia*, *133*(6), 1234–1249. https://doi.org/10.1016/j.bja.2024.08.009
11. Cetin, M., Brown, C. S., Bellolio, F., Drapkin, J., Glatter, R., Motov, S., & E Silva, L. O. J. (2025). Nebulized ketamine for acute pain management in the Emergency Department: A systematic review and meta-analysis. *The American Journal of Emergency Medicine*, *94*, 110–118. https://doi.org/10.1016/j.ajem.2025.04.051
12. Chah, N., Jones, M., Milord, S., Al-Eryani, K., & Enciso, R. (2021). Efficacy of ketamine in the treatment of migraines and other unspecified primary headache disorders compared to placebo and other interventions: A systematic review. *Journal of Dental Anesthesia and Pain Medicine*, *21*(5), 413–429. https://doi.org/10.17245/jdapm.2021.21.5.413
13. Chan, E. O. T., Chan, V. W. S., Tang, T. S. T., Cheung, V., Wong, M. C. S., Yee, C. H., Ng, C. F., & Teoh, J. Y. C. (2022). Systematic review and meta-analysis of ketamine-associated uropathy. *Hong Kong Medical Journal = Xianggang Yi Xue Za Zhi*, *28*(6), 466–474. https://doi.org/10.12809/hkmj209194
14. Chou, X., Zha, W., Hu, J., Chen, C., Singh, R. K., & Liu, G. (2025). Unlocking the Potential of Ketamine: A Systematic Review and Meta-analysis of its Safety and Efficacy in Acute Pain Management. *Combinatorial Chemistry & High Throughput Screening*. https://doi.org/10.2174/0113862073377616250404101442
15. Ciccarone, D. (2021). The Rise of Illicit Fentanyls, Stimulants and the Fourth Wave of the Opioid Overdose Crisis. *Current Opinion in Psychiatry*, *34*(4), 344–350. https://doi.org/10.1097/YCO.0000000000000717
16. Clements, J. A., Nimmo, W. S., & Grant, I. S. (1982). Bioavailability, Pharmacokinetics, and Analgesic Activity of Ketamine in Humans. *Journal of Pharmaceutical Sciences*, *71*(5), 539–542. https://doi.org/10.1002/jps.2600710516
17. Coffee, Z., Cheng, K., Slebodnik, M., Mulligan, K., Yu, C. H., Vanderah, T. W., & Gordon, J. S. (2024). The Impact of Nonpharmacological Interventions on Opioid Use for Chronic Noncancer Pain: A Scoping Review. *International Journal of Environmental Research and Public Health*, *21*(6), 794. https://doi.org/10.3390/ijerph21060794
18. Cohen, S. P., Bhatia, A., Buvanendran, A., Schwenk, E. S., Wasan, A. D., Hurley, R. W., Viscusi, E. R., Narouze, S., Davis, F. N., Ritchie, E. C., Lubenow, T. R., & Hooten, W. M. (2018). Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Regional Anesthesia and Pain Medicine*, *43*(5), 521–546. https://doi.org/10.1097/AAP.0000000000000808
19. Culp, C., Kim, H. K., & Abdi, S. (2020). Ketamine Use for Cancer and Chronic Pain Management. *Frontiers in Pharmacology*, *11*, 599721. https://doi.org/10.3389/fphar.2020.599721
20. Dagher, C., Mattar, R., Aoun, M., Tohme, J., Naccache, N., & Jabbour, H. (2025). Opioid-free anesthesia in bariatric surgery: A prospective randomized controlled trial. *European Journal of Medical Research*, *30*, 320. https://doi.org/10.1186/s40001-025-02565-9
21. Daly, E. J., Singh, J. B., Fedgchin, M., Cooper, K., Lim, P., Shelton, R. C., Thase, M. E., Winokur, A., Van Nueten, L., Manji, H., & Drevets, W. C. (2018). Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression. *JAMA Psychiatry*, *75*(2), 139–148. https://doi.org/10.1001/jamapsychiatry.2017.3739
22. de Carvalho, J. F., & de Sena, E. P. (2024). Ketamine in fibromyalgia: A systematic review. *Advances in Rheumatology*, *64*(1), 54. https://doi.org/10.1186/s42358-024-00393-9
23. de León-López, C. A. M., Carretero-Rey, M., & Khan, Z. U. (2025). AMPA Receptors in Synaptic Plasticity, Memory Function, and Brain Diseases. *Cellular and Molecular Neurobiology*, *45*(1), 14. https://doi.org/10.1007/s10571-024-01529-7
24. *Drug Approval Package: Spravato*. (n.d.). Retrieved 27 November 2025, from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000TOC.cfm
25. Duman, R. S., Aghajanian, G. K., Sanacora, G., & Krystal, J. H. (2016). Synaptic plasticity and depression: New insights from stress and rapid-acting antidepressants. *Nature Medicine*, *22*(3), 238–249. https://doi.org/10.1038/nm.4050
26. Fassio, A., Mantovani, A., Gatti, D., Rossini, M., Viapiana, O., Gavioli, I., Benini, C., & Adami, G. (2022). Pharmacological treatment in adult patients with CRPS-I: A systematic review and meta-analysis of randomized controlled trials. *Rheumatology (Oxford, England)*, *61*(9), 3534–3546. https://doi.org/10.1093/rheumatology/keac060
27. Finch, P. M., Knudsen, L., & Drummond, P. D. (2009). Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. *Pain*, *146*(1–2), 18–25. https://doi.org/10.1016/j.pain.2009.05.017

28. Garland, E. L. (2014). Treating chronic pain: The need for non-opioid options. *Expert Review of Clinical Pharmacology*, *7*(5), 545–550. https://doi.org/10.1586/17512433.2014.928587
29. Guimarães Pereira, J. E., Ferreira Gomes Pereira, L., Mercante Linhares, R., Darcy Alves Bersot, C., Aslanidis, T., & Ashmawi, H. A. (2022). Efficacy and Safety of Ketamine in the Treatment of Neuropathic Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of Pain Research*, *15*, 1011–1037. https://doi.org/10.2147/JPR.S358070
30. Guo, J., Zhao, F., Bian, J., Hu, Y., & Tan, J. (2024). Low-dose ketamine versus morphine in the treatment of acute pain in the emergency department: A meta-analysis of 15 randomized controlled trials. *The American Journal of Emergency Medicine*, *76*, 140–149. https://doi.org/10.1016/j.ajem.2023.11.056
31. Hannon, C. P., Fillingham, Y. A., Gililland, J. M., Sporer, S. M., Casambre, F. D., Verity, T. J., Woznica, A., Nelson, N., Hamilton, W. G., & Della Valle, C. J. (2023). A Systematic Review of the Efficacy and Safety of Ketamine in Total Joint Arthroplasty. *The Journal of Arthroplasty*, *38*(4), 763-768.e2. https://doi.org/10.1016/j.arth.2022.10.037
32. Haroz, E. E., Ritchey, M., Bass, J. K., Kohrt, B. A., Augustinavicius, J., Michalopoulos, L., Burkey, M. D., & Bolton, P. (2017). How is depression experienced around the world? A systematic review of qualitative literature. *Social Science & Medicine (1982)*, *183*, 151–162. https://doi.org/10.1016/j.socscimed.2016.12.030
33. Hashimoto, K. (2019). Rapid-acting antidepressant ketamine, its metabolites and other candidates: A historical overview and future perspective. *Psychiatry and Clinical Neurosciences*, *73*(10), 613–627. https://doi.org/10.1111/pcn.12902
34. He, Z., Wu, J., Yang, C., & Jiang, P. (2025). Effects of perioperative intravenous esketamine on postoperative recovery quality in adult patients: A systematic review and meta-analysis. *PeerJ*, *13*, e19977. https://doi.org/10.7717/peerj.19977
35. Heinz, P., Geelhoed, G. C., Wee, C., & Pascoe, E. M. (2006). Is atropine needed with ketamine sedation? A prospective, randomised, double blind study. *Emergency Medicine Journal: EMJ*, *23*(3), 206–209. https://doi.org/10.1136/emj.2005.028969
36. Herrman, H., Patel, V., Kieling, C., Berk, M., Buchweitz, C., Cuijpers, P., Furukawa, T. A., Kessler, R. C., Kohrt, B. A., Maj, M., McGorry, P., Reynolds, C. F., Weissman, M. M., Chibanda, D., Dowrick, C., Howard, L. M., Hoven, C. W., Knapp, M., Mayberg, H. S., … Wolpert, M. (2022). Time for united action on depression: A Lancet-World Psychiatric Association Commission. *Lancet (London, England)*, *399*(10328), 957–1022. https://doi.org/10.1016/S0140-6736(21)02141-3
37. Hess, E. M., Riggs, L. M., Michaelides, M., & Gould, T. D. (2022). Mechanisms of Ketamine and its Metabolites as Antidepressants. *Biochemical Pharmacology*, *197*, 114892. https://doi.org/10.1016/j.bcp.2021.114892
38. Hill, S. (2004). Pharmacokinetics of drug infusions. *Continuing Education in Anaesthesia Critical Care & Pain*, *4*(3), 76–80. https://doi.org/10.1093/bjaceaccp/mkh021
39. Hirota, K., & Lambert, D. G. (2022). Ketamine; history and role in anesthetic pharmacology. *Neuropharmacology*, *216*, 109171. https://doi.org/10.1016/j.neuropharm.2022.109171
40. Hirschfeld, R. M. (2000). History and evolution of the monoamine hypothesis of depression. *The Journal of Clinical Psychiatry*, *61 Suppl 6*, 4–6.
41. Hooten, W. M. (2016). Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. *Mayo Clinic Proceedings*, *91*(7), 955–970. https://doi.org/10.1016/j.mayocp.2016.04.029
42. *ICD-10 Version:2019*. (n.d.). Retrieved 27 November 2025, from https://icd.who.int/browse10/2019/en#/F10-F19
43. Iob, E., Kirschbaum, C., & Steptoe, A. (2020). Persistent depressive symptoms, HPA-axis hyperactivity, and inflammation: The role of cognitive-affective and somatic symptoms. *Molecular Psychiatry*, *25*(5), 1130–1140. https://doi.org/10.1038/s41380-019-0501-6
44. Ionescu, D. F., Fu, D.-J., Qiu, X., Lane, R., Lim, P., Kasper, S., Hough, D., Drevets, W. C., Manji, H., & Canuso, C. M. (2020). Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *International Journal of Neuropsychopharmacology*, *24*(1), 22–31. https://doi.org/10.1093/ijnp/pyaa068
45. Jewett, B. E., & Thapa, B. (2025). Physiology, NMDA Receptor. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK519495/
46. Jiao, J., Fan, J., Zhang, Y., & Chen, L. (2024). Efficacy and Safety of Ketamine to Treat Cancer Pain in Adult Patients: A Systematic Review. *Journal of Pain and Symptom Management*, *67*(3), e185–e210. https://doi.org/10.1016/j.jpainsymman.2023.11.004
47. Kalsi, S. S., Wood, D. M., & Dargan, P. I. (2011). The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. *Emerging Health Threats Journal*, *4*, 10.3402/ehtj.v4i0.7107. https://doi.org/10.3402/ehtj.v4i0.7107
48. Kim, J.-W., Suzuki, K., Kavalali, E. T., & Monteggia, L. M. (2024). Ketamine: Mechanisms and Relevance to Treatment of Depression. *Annual Review of Medicine*, *75*(1), 129–143. https://doi.org/10.1146/annurev-med-051322-120608

49. Kiraly, D. D., Horn, S. R., Van Dam, N. T., Costi, S., Schwartz, J., Kim-Schulze, S., Patel, M., Hodes, G. E., Russo, S. J., Merad, M., Iosifescu, D. V., Charney, D. S., & Murrough, J. W. (2017). Altered peripheral immune profiles in treatment-resistant depression: Response to ketamine and prediction of treatment outcome. *Translational Psychiatry*, *7*(3), e1065. https://doi.org/10.1038/tp.2017.31
50. Kohtala, S. (2021). Ketamine—50 years in use: From anesthesia to rapid antidepressant effects and neurobiological mechanisms. *Pharmacological Reports*, *73*(2), 323–345. https://doi.org/10.1007/s43440-021-00232-4
51. Koolschijn, P. C. M. P., van Haren, N. E. M., Lensvelt-Mulders, G. J. L. M., Hulshoff Pol, H. E., & Kahn, R. S. (2009). Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. *Human Brain Mapping*, *30*(11), 3719–3735. https://doi.org/10.1002/hbm.20801
52. Li, N., Lee, B., Liu, R.-J., Banasr, M., Dwyer, J. M., Iwata, M., Li, X.-Y., Aghajanian, G., & Duman, R. S. (2010). mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science (New York, N.Y.)*, *329*(5994), 959–964. https://doi.org/10.1126/science.1190287
53. Marinus, J., Moseley, G. L., Birklein, F., Baron, R., Maihöfner, C., Kingery, W. S., & van Hilten, J. J. (2011). Clinical features and pathophysiology of complex regional pain syndrome. *The Lancet. Neurology*, *10*(7), 637–648. https://doi.org/10.1016/S1474-4422(11)70106-5
54. Marongiu, S., van Eijk, M., Gresnigt, F. M. J., Croes, E. A., & Franssen, E. J. F. (2025). Rising incidence of recreational ketamine use: Clinical cases and management in emergency settings. *Toxicology Reports*, *14*, 101940. https://doi.org/10.1016/j.toxrep.2025.101940
55. Martinotti, G., Chiappini, S., Pettorruso, M., Mosca, A., Miuli, A., Di Carlo, F., D'Andrea, G., Collevecchio, R., Di Muzio, I., Sensi, S. L., & Di Giannantonio, M. (2021). Therapeutic Potentials of Ketamine and Esketamine in Obsessive–Compulsive Disorder (OCD), Substance Use Disorders (SUD) and Eating Disorders (ED): A Review of the Current Literature. *Brain Sciences*, *11*(7), 856. https://doi.org/10.3390/brainsci11070856
56. Meyer-Frießem, C. H., Lipke, E., Weibel, S., Kranke, P., Reichl, S., Pogatzki-Zahn, E. M., Zahn, P. K., & Schnabel, A. (2022). Perioperative ketamine for postoperative pain management in patients with preoperative opioid intake: A systematic review and meta-analysis. *Journal of Clinical Anesthesia*, *78*, 110652. https://doi.org/10.1016/j.jclinane.2022.110652
57. Morgan, C. J. A., Curran, H. V., & Independent Scientific Committee on Drugs. (2012). Ketamine use: A review. *Addiction (Abingdon, England)*, *107*(1), 27–38. https://doi.org/10.1111/j.1360-0443.2011.03576.x
58. Niesters, M., Martini, C., & Dahan, A. (2014). Ketamine for chronic pain: Risks and benefits. *British Journal of Clinical Pharmacology*, *77*(2), 357–367. https://doi.org/10.1111/bcp.12094
59. Oye, I., Paulsen, O., & Maurset, A. (1992). Effects of ketamine on sensory perception: Evidence for a role of N-methyl-D-aspartate receptors. *The Journal of Pharmacology and Experimental Therapeutics*, *260*(3), 1209–1213.
60. Pai, A., & Heining, M. (2007). Ketamine. *Continuing Education in Anaesthesia, Critical Care and Pain*, *7*. https://doi.org/10.1093/bjaceaccp/mkm008
61. Patanwala, A. E., Martin, J. R., & Erstad, B. L. (2017). Ketamine for Analgosedation in the Intensive Care Unit: A Systematic Review. *Journal of Intensive Care Medicine*, *32*(6), 387–395. https://doi.org/10.1177/0885066615620592
62. Peltoniemi, M. A., Hagelberg, N. M., Olkkola, K. T., & Saari, T. I. (2016). Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. *Clinical Pharmacokinetics*, *55*(9), 1059–1077. https://doi.org/10.1007/s40262-016-0383-6
63. Pourmand, A., Mazer-Amirshahi, M., Royall, C., Alhawas, R., & Shesser, R. (2017). Low dose ketamine use in the emergency department, a new direction in pain management. *The American Journal of Emergency Medicine*, *35*(6), 918–921. https://doi.org/10.1016/j.ajem.2017.03.005
64. Price, R. B., & Duman, R. (2020). Neuroplasticity in cognitive and psychological mechanisms of depression: An integrative model. *Molecular Psychiatry*, *25*(3), 530–543. https://doi.org/10.1038/s41380-019-0615-x
65. Reede, K., Bartholomew, R., Nielsen, D., Ahmeti, M., & Zreik, K. (2023). Ketamine in Trauma: A Literature Review and Administration Guidelines. *Cureus*, *15*(11), e48099. https://doi.org/10.7759/cureus.48099
66. Riccardi, A., Guarino, M., Serra, S., Spampinato, M. D., Vanni, S., Shiffer, D., Voza, A., Fabbri, A., & De Iaco, F. (2023). Narrative Review: Low-Dose Ketamine for Pain Management. *Journal of Clinical Medicine*, *12*(9), 3256. https://doi.org/10.3390/jcm12093256
67. Richards, N. D., Howell, S. J., Bellamy, M. C., & Beck, J. (2025). The diverse effects of ketamine, jack-of-all-trades: A narrative review. *BJA: British Journal of Anaesthesia*, *134*(3), 649–661. https://doi.org/10.1016/j.bja.2024.11.018
68. Schwenk, E. S., Torjman, M. C., Moaddel, R., Lovett, J., Katz, D., Denk, W., Lauritsen, C., Silberstein, S. D., & Wainer, I. W. (2021). Ketamine for Refractory Chronic Migraine: An Observational Pilot Study and Metabolite Analysis. *Journal of Clinical Pharmacology*, *61*(11), 1421–1429. https://doi.org/10.1002/jcph.1920
69. Schwenk, E. S., Viscusi, E. R., Buvanendran, A., Hurley, R. W., Wasan, A. D., Narouze, S., Bhatia, A., Davis, F. N., Hooten, W. M., & Cohen, S. P. (2018). Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Regional Anesthesia and Pain Medicine*, *43*(5), 456–466. https://doi.org/10.1097/AAP.0000000000000806

70. Shekarsarai, C., McQuibban, N. A., & Gullick, N. (2025). The Analgesic Efficacy of Therapies Used for Complex Regional Pain Syndrome: A Systematic Review. *Cureus*, *17*(9), e91697. https://doi.org/10.7759/cureus.91697
71. Singh, J. B., Fedgchin, M., Daly, E., Xi, L., Melman, C., Bruecker, G. D., Tadic, A., Sienaert, P., Wiegand, F., Manji, H., Drevets, W. C., & Nueten, L. V. (2016). Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study. *Biological Psychiatry*, *80*(6), 424–431. https://doi.org/10.1016/j.biopsych.2015.10.018
72. Subramanian, S., Haroutounian, S., Palanca, B. J. A., & Lenze, E. J. (2022). Ketamine as a therapeutic agent for depression and pain: Mechanisms and evidence. *Journal of the Neurological Sciences*, *434*. https://doi.org/10.1016/j.jns.2022.120152
73. Taylor, A. M. W., Becker, S., Schweinhardt, P., & Cahill, C. (2016). Mesolimbic dopamine signaling in acute and chronic pain: Implications for motivation, analgesia, and addiction. *Pain*, *157*(6), 1194–1198. https://doi.org/10.1097/j.pain.0000000000000494
74. Tékus, V., Borbély, É., Goebel, A., Baron, R., Hajna, Z., & Helyes, Z. (2025). Novel approaches for drug development against chronic primary pain: A systematic review. *British Journal of Pharmacology*. https://doi.org/10.1111/bph.70228
75. Tiger, M., Veldman, E. R., Ekman, C.-J., Halldin, C., Svenningsson, P., & Lundberg, J. (2020). A randomized placebo-controlled PET study of ketamine´s effect on serotonin1B receptor binding in patients with SSRI-resistant depression. *Translational Psychiatry*, *10*, 159. https://doi.org/10.1038/s41398-020-0844-4
76. Torrico, T. J., & Abdijadid, S. (2025). Neuroanatomy, Limbic System. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK538491/
77. Treadway, M. T., Waskom, M. L., Dillon, D. G., Holmes, A. J., Park, M. T. M., Chakravarty, M. M., Dutra, S. J., Polli, F. E., Iosifescu, D. V., Fava, M., Gabrieli, J. D. E., & Pizzagalli, D. A. (2015). Illness Progression, Recent Stress and Morphometry of Hippocampal Subfields and Medial Prefrontal Cortex in Major Depression. *Biological Psychiatry*, *77*(3), 285–294. https://doi.org/10.1016/j.biopsych.2014.06.018
78. Varas, V., Bertinelli, P., Carrasco, P., Souper, N., Álvarez, P., Danilla, S., Egaña, J. I., Penna, A., Sepúlveda, S., Arancibia, V., Álvarez, M. G., & Vergara, R. (2020). Intraoperative Ketamine and Magnesium Therapy to Control Postoperative Pain After Abdominoplasty and/or Liposuction: A Clinical Randomized Trial. *Journal of Pain Research*, *13*, 2937–2946. https://doi.org/10.2147/JPR.S276710
79. Weiner, A. L., Vieira, L., McKay, C. A., & Bayer, M. J. (2000). Ketamine abusers presenting to the Emergency Department: A case series. *Journal of Emergency Medicine*, *18*(4), 447–451. https://doi.org/10.1016/S0736-4679(00)00162-1
80. White, P. F., Schüttler, J., Shafer, A., Stanski, D. R., Horai, Y., & Trevor, A. J. (1985). COMPARATIVE PHARMACOLOGY OF THE KETAMINE ISOMERS. *British Journal of Anaesthesia*, *57*(2), 197–203. https://doi.org/10.1093/bja/57.2.197
81. Williams, N. R., Heifets, B. D., Blasey, C., Sudheimer, K., Pannu, J., Pankow, H., Hawkins, J., Birnbaum, J., Lyons, D. M., Rodriguez, C. I., & Schatzberg, A. F. (2018). Opioid Receptor Antagonism Attenuates Antidepressant Effects of Ketamine. *The American Journal of Psychiatry*, *175*(12), 1205–1215. https://doi.org/10.1176/appi.ajp.2018.18020138
82. Wu, H., Savalia, N. K., & Kwan, A. C. (2021). Ketamine for a boost of neural plasticity: How, but also when? *Biological Psychiatry*, *89*(11), 1030–1032. https://doi.org/10.1016/j.biopsych.2021.03.014
83. Wu, M., Minkowicz, S., Dumrongprechachan, V., Hamilton, P., & Kozorovitskiy, Y. (2021). Ketamine rapidly enhances glutamate-evoked dendritic spinogenesis in medial prefrontal cortex through dopaminergic mechanisms. *Biological Psychiatry*, *89*(11), 1096–1105. https://doi.org/10.1016/j.biopsych.2020.12.022
84. Xiang, J., Cao, C., Chen, J., Kong, F., Nian, S., Li, Z., & Li, N. (2024). Efficacy and safety of ketamine as an adjuvant to regional anesthesia: A systematic review and meta-analysis of randomized controlled trials. *Journal of Clinical Anesthesia*, *94*, 111415. https://doi.org/10.1016/j.jclinane.2024.111415
85. Ying, M., & Zuo, Y. (2023). Efficacy of Low-dose Ketamine for Control of Acute Pain in the Emergency Setting: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Western Journal of Emergency Medicine*, *24*(3), 644–653. https://doi.org/10.5811/westjem.2023.2.58368
86. Yuan, H., Natekar, A., Park, J., Lauritsen, C. G., Viscusi, E. R., & Marmura, M. J. (2023). Real-world study of intranasal ketamine for use in patients with refractory chronic migraine: A retrospective analysis. *Regional Anesthesia and Pain Medicine*, *48*(12), 581–587. https://doi.org/10.1136/rapm-2022-104223
87. Zanos, P., Moaddel, R., Morris, P. J., Riggs, L. M., Highland, J. N., Georgiou, P., Pereira, E. F. R., Albuquerque, E. X., Thomas, C. J., Zarate, C. A., & Gould, T. D. (2018). Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacological Reviews*, *70*(3), 621–660. https://doi.org/10.1124/pr.117.015198
88. Zawilska, J. B., & Zwierzyńska, E. (2024). Ketamine—Precursor of a new generation antidepressant drugs. *Farmacja Polska*, *80*(1), 51–62. https://doi.org/10.32383/farmpol/186596
89. Zhang, X., Duan, P., Sun, Y., & Na, Q. (2025). Effect of low-dose esketamine on cardio-biliary reflex and postoperative pain during laparoscopic cholecystectomy surgery: A randomized, controlled trail. *PloS One*, *20*(5), e0321892. https://doi.org/10.1371/journal.pone.0321892