Repurposing Potential of Ketamine: Opportunities and Challenges

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ABSTRACT

Ketamine is a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor which also interacts with various other receptors that account for its myriad actions. Originally approved as a general anesthetic, it is being explored to be repurposed for numerous other indications such as depressive disorders, suicidal ideation, substance-use disorders, anxiety disorders, chronic pain, refractory status epilepticus, and bronchial asthma exacerbations. Numerous trials are ongoing for the same. The nasal spray of esketamine, a more potent S (+) enantiomer of ketamine, has been approved by the United States Food and Drug Administration (USFDA) for treatment-resistant depression along with the oral antidepressants. However, there are concerns about its safety on long term use, given its psychedelic effects and potential abuse. In this review, we discuss repurposing ketamine for potential therapeutic use and about the safety concerns related to ketamine and esketamine.

Key words: Depression, esketamine, repurposing, safety

Ketamine, a phencyclidine derivative, was developed in the year 1962 to overcome the psychotomimetic side effects and abuse potential of the parent drug phencyclidine.\(^1\) It is a racemic mixture of two enantiomers S (+) and R (–), and its S isomer esketamine is more potent than the racemate ketamine having fewer side effects.\(^2\) It was approved in 1970 by the United States Food and Drug Administration (USFDA) for use in humans as an intravenous anesthetic agent.\(^3\) Drug repurposing or re-profiling, for new potential therapeutic areas, holds a great advantage over conventional drug development in reducing the cost, saving time, and the requirement of less data since such candidates have already undergone the tests for toxicity and regulatory work-up.\(^4\)

Ketamine, a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptor, acts on numerous other receptors, contributing to its legion effects and uses. It has antagonistic actions at L-type, voltage-gated Ca\(^{2+}\) channels; nicotinic and muscarinic acetylcholine receptors; hyperpolarization-activated cyclic nucleotide-gated (HCN) channels; voltage-sensitive sodium channels, and large-conductance, K\(_{Ca}\) channels.
channels (BK channels). Also, it causes activation of μ and δ opioid, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, (AMPA) and γ-aminobutyric acid A (GABA_A) receptors.\[31\]

This review article focuses on the repurposing potential of ketamine, its therapeutic uses and the safety concerns related to ketamine and esketamine.

The current evidence and ongoing trials available regarding the use of ketamine in various approved and potential therapeutic indications are given in Table 1. Given its myriad actions and great repurposing potential, it is approved or is being investigated for the following conditions.

**Analgesia**

Ketamine is an agent used for induction of general anesthesia, particularly in patients who are hemodynamically unstable or having bronchospasm, and in geriatric and pediatric patients.\[32\] It is used in doses 0.5–1.5 mg/kg intravenously (i.v.), 4–6 mg/kg intramuscularly (i.m.), and 8–10 mg/kg per rectum for induction, and as an i.v. infusion of 25–100 μg/kg/minute for maintenance of anesthesia.\[6] It produces profound analgesia, amnesia, and unresponsiveness to commands but does not produce complete unconsciousness (dissociative anesthesia). (S)–ketamine also induces sedation at doses 3–9 mg/kg intranasally.\[7\]

In subanesthetic doses, ketamine is an effective analgesic for postoperative pain. It is efficacious for management of high levels of chronic as well as acute postoperative pain in doses 0.15–0.25 mg/kg i.v. It also reduces the opioid requirement in these patients.\[5\] Further, preliminary evidence suggests that ketamine may also be used in these doses for acute post-traumatic pain management as an alternative to opioids.\[9\]

It is used as a third-line drug or adjuvant for cancer pain not responding to standard drugs like opioids, amitriptyline, gabapentin, and nonsteroidal antiinflammatory drugs. However, evidence regarding its efficacy and safety in cancer pain is insufficient.\[10-13\] A Phase I/Phase II, prospective, single-group, open-label clinical trial (NCT03146806)\[14\] is recruiting participants to evaluate the safety and utility of intranasally administered ketamine for the treatment of cancer pain. A phase II single-arm, open-label trial to evaluate the effectiveness of continuous intravenous infusion of ketamine in terminally ill cancer patients is in the patient recruitment stage (NCT03362073).\[15\]

Ketamine is also used as an adjuvant drug for intractable chronic noncancer pain, complex regional pain syndrome (CRPS), and refractory neuropathic pain.\[16-18\] NMDA antagonism in the brain and spinal cord is the main mechanism of its analgesic effect.

**Table 1: Current evidence for the repurposing potential of ketamine**

| Approved/Potential Therapeutic Use | Proposed Mechanism of Action | Evidence |
|-----------------------------------|------------------------------|----------|
| Cancer pain                       | NMDA antagonism in the brain and spinal cord | Laureneti et al., 1999\[40\] Finkell et al., 2007\[51\] |
| Treatment Resistant Depression*   | Increase in the signaling of mTOR, increased protein synthesis via dephosphorylation of eukaryotic translation elongation factor 2 and increase in BDNF, TrkB and GSK-3-associated pathways in TRD | Murrough et al., 2013\[72\] Philips et al., 2019\[46\] Zhang et al., 2019\[73\] Singh et al., 2016\[47\] Dalry et al., 2017\[31\]* |
| Cocaine Use Disorder              | Improved prefrontal cortex glutamate homeostasis causing synaptic improvements | Dakwar et al., 2017\[30\] |
| Opioid Use Disorder               | Improved prefrontal cortex glutamate homeostasis, causing synaptic improvements | Krupitsky et al., 2002\[44\] Krupitsky et al., 2007\[70\] Jovaisa et al., 2006\[43\] |
| Alcohol Use Disorder              | Improved prefrontal cortex glutamate homeostasis, causing synaptic improvements | Wong et al., 2015\[41\] |
| Suicidal Ideation                 | Increased signaling via mTOR, BDNF and GSK-3 pathways | Canuso et al., 2018\[45\] Grunebaum et al., 2018\[46\] Grunebaum et al., 2017\[73\] Fan et al., 2017\[74\] |
| Anxiety Disorders (SAD, GAD)      | Increased BDNF signaling in hippocampus | Taylor et al., 2018\[75\] Glue et al., 2018\[41\] |
| Refractory Status Epileptics      | NMDA antagonism and reduction in NMDA induced neurotoxicity | Rosati et al., 2012\[82\] Ivento et al., 2015\[42\] |
| Bronchial Asthma                  | Inhibition of inflammatory cascade, reduction in markers of inflammation and bronchodilatation | Esmailian et al., 2018\[87\] Tiwari et al., 2016\[48\] |

* Esketamine has been recently approved for use in patients with treatment resistant depression. BDNF – Brain-derived neurotrophic factor, GAD – Generalized anxiety disorder, GSK-3 – Glycogen synthase kinase-3, mTOR – Mammalian target of rapamycin, NMDA – N-methyl-D-aspartate, SAD – Social anxiety disorder; TRD – Treatment resistant depression, TrkB – Tropomysin-related kinase B
Ketamine increases the inhibitory serotonergic signal and thus enhances the endogenous antinociceptive system.\[^{[19]}\]

**Depressive disorders**

Ketamine has shown a rapid antidepressant response in the treatment of unipolar depression and treatment-resistant depression (TRD).\[^{[20]}\] Its action is seen within 24 hours, lasting for 4–7 days (transient effect) after single intravenous administration of subanesthetic doses (0.5 mg/kg). High response rates with minimal side effects are observed with its use.\[^{[21,22]}\] Further, it was observed that with the administration of repeated (six) infusions of ketamine to patients of TRD, cumulative and sustained antidepressant effects were obtained.\[^{[23,24]}\] In a meta-analysis of randomized controlled trials (RCTs), ketamine given along with other anesthetic agents conferred a short term improvement in patients at early stages of electroconvulsive therapy (ECT).\[^{[25]}\] However, ketamine has shown low antidepressant efficacy in elderly, with mild and transient adverse effects.\[^{[26]}\]

Probable mechanisms responsible for rapid antidepressant effects of ketamine are increase in the signalling of mammalian target of rapamycin (mTOR), increased protein synthesis via dephosphorylation of eukaryotic translation elongation factor 2, and increase in brain-derived neurotrophic factor (BDNF). Various pathways associated with the action of ketamine are tropomyosin-related kinase B (TrkB) pathway, associated downstream phosphatidylinositol-3-kinase (PI3K)-Akt pathway, and glycogen synthase kinase-3 (GSK-3)-associated pathways. Enhanced glutamate signalling via the AMPA receptors in the prefrontal cortical regions and subsequent increase in synaptogenesis and synaptic functioning also contribute to its antidepressant effects.\[^{[27,28]}\]

A phase III randomized, initially double-blind, then open-label clinical trial (NCT03742557),\[^{[29]}\] aimed to provide clinical evidence of responses in the form of neurological basis or underlying biomarkers of response after a series of ketamine administrations in patients with TRD, is currently in recruitment stage. Another phase II single-arm open-label trial evaluating the cortical neurophysiological functions after ketamine administration in patients of TRD is also in progress (NCT02935595).\[^{[30]}\] Recently, Esketamine nasal spray has been approved by the USFDA for TRD. Esketamine, due to its safety concerns and potential for misuse and abuse will be available only through a restricted distribution system. Moreover, it is to be self-administered under the supervision of a healthcare provider, and the patient must be monitored for at least two hours after the dose due to the risk of sedation and dissociation.\[^{[31]}\]

Esketamine is more potent, 0.40 mg/kg i.v. dose as comparable to 0.5 mg/kg i.v. ketamine. Antidepressant efficacy of intravenous esketamine is demonstrable at doses 0.2 mg/kg and 0.4 mg/kg, with better tolerability at low doses.\[^{[32]}\] A recent clinical trial has demonstrated the rapid antidepressant effects of intranasal esketamine in patients of TRD in doses 56 mg and 84 mg and a safety profile comparable to i.v. ketamine.\[^{[33]}\] A randomized, double-blind, non inferiority clinical trial making a neck to neck comparison of antidepressant efficacy of single intravenous infusion of 0.25 mg esketamine and 0.5 mg ketamine in patients with TRD is ongoing.\[^{[34]}\] Current antidepressants take around 2–3 weeks for producing a response, and remission is seen in around 70% of patients (30% of patients did not respond).\[^{[35]}\] Therefore, a rapid action of esketamine could be useful. Intranasal esketamine has also shown a transient impairment of cognitive performance in healthy individuals, which is manifested as slow performance time or with more rate of causing errors\[^{[36]}\] and it has been given a black boxed warning regarding risk for sedation; difficulty with attention, judgment, and thinking (dissociation); abuse, and suicidal thoughts, and behavior.\[^{[31]}\]

**Substance use disorders (SUDs)**

Ketamine has been found to be efficacious in cocaine, heroin, and alcohol use disorders. In cocaine-dependent participants, ketamine (0.41 mg/kg) significantly increased the motivation to quit cocaine compared to lorazepam and also caused a significant reduction in cocaine craving.\[^{[37]}\] Ketamine also caused a significant reduction (66%) in the rates of cocaine self-administration.\[^{[38]}\] A phase III, randomized, double-blind, placebo-controlled trial (NCT03344419) is being conducted to evaluate the efficacy of ketamine infusion in cocaine use disorder is recruiting participants.\[^{[39]}\]

High-dose ketamine (2 mg/kg) showed statistically significant improvement in the abstinence rates and reduced craving in patients with heroin dependence and nearly double the participants showed abstinence up to one year after multiple doses (up to three) as compared to a single dose of ketamine.\[^{[40,41]}\] Ketamine effectively suppresses the physiological response to opioid withdrawal by decreasing mean arterial pressure, heart rate, and serum cortisol levels.\[^{[42]}\] A phase III randomized controlled trial NCT03345173, in the recruiting stage, will evaluate the efficacy of ketamine in facilitating rapid naltrexone induction for acute detoxification of opioid users.\[^{[43]}\]
It also improved the one year abstinence in patients of alcohol use disorder.\cite{144} Ketamine reduced the requirement of benzodiazepines when used as an adjunct to them in the management of alcohol withdrawal symptoms.\cite{145} Two Phase-2, placebo-controlled RCTs, NCT02649231 and NCT02461927, evaluating the efficacy of ketamine in alcohol use disorder are presently recruiting participants.\cite{146,147}

**Suicidal ideation**

Ketamine, as well as esketamine, were found to be efficacious in reducing suicidal ideation and behavior in patients of major depression, bipolar disorder, and cancer. A single i.v. administration of sub anesthetic dose (0.5 mg/kg) ketamine produces rapid amelioration of suicidal thoughts and behavior within few hours, with sustained effect up to a week. Beneficial effects of ketamine have been observed for up to 6 weeks when combined with standard pharmacotherapy.\cite{20,48-50} Although these results seem promising, psychotomimetic side effects and concerns regarding long term use of ketamine have to be kept in mind. An RCT (NCT01892995), yet to start recruiting, has been planned to evaluate the effect of ketamine in patients with acute suicidal ideation.\cite{51} Another phase III RCT (NCT02418702), still in the prerecruitment phase, will evaluate the effect of ketamine on suicidal thinking of military persons.\cite{52}

**Anxiety disorders**

The anxiolytic effects of ketamine in patients of major depression have been elucidated.\cite{53,54} In a randomized, double-blind placebo-controlled trial in patients of a social anxiety disorder (SAD), it was observed that ketamine infusion, compared to placebo, showed a significant benefit in SAD symptoms in the first 14 days.\cite{55} However, there is a need for active (e.g., midazolam) controlled trials to substantiate the anxiolytic effects and optimal dosing of ketamine. Weekly doses of ketamine 1 mg/kg given subcutaneously were well tolerated, and the dissociative symptoms were found to decrease after repeated dosing, thus helpful in maintenance of SAD.\cite{56} Mechanism of its anti-anxiety effect is similar to that of its anti depressant effect, i.e., by activating synaptic plasticity, by increasing BDNF translation and secretion, and by inhibiting GSK-3, and activating mTOR signaling.\cite{56,57}

A phase IV, midazolam controlled clinical trial (NCT02579928)\cite{58} to evaluate the tolerability and short-term efficacy of ketamine for adolescents with medication refractory anxiety disorders (SAD, panic disorders, generalized anxiety disorder [GAD] and/or separation anxiety disorder) is currently ongoing.

Another phase IV, double-blind RCT (NCT03043430)\cite{59} is in progress (in recruiting stage) to evaluate the efficacy of intranasal ketamine for anxiolysis in pediatric patients.

**Refractory status epilepticus**

Evidence suggests that the activity as well as the number of NMDA receptors is increased in refractory status epilepsy. Ketamine reduces NMDA receptor-induced neurotoxicity and also has a neuroprotective role; hence, it could be effective for the treatment of refractory convulsive status epilepticus (RCSE).\cite{59,60} Evidence also suggests that ketamine, at usual doses, has an epileptogenic potential and should be avoided in patients with epilepsy.\cite{61}

In a small, open-label, uncontrolled study, it was observed that ketamine appears effective and safe for the treatment of status epilepticus in children.\cite{62} However, large scale controlled trials are required to substantiate these findings.\cite{63} Ketamine can be effectively used to treat RCSE as an alternative to general anesthetics and also avoids the need for endotracheal intubation in these patients.\cite{64}

A phase III RCT (NCT02431663)\cite{64} has been planned to evaluate the efficacy of intravenous administration of ketamine in children with RCSE while NCT03115489,\cite{65} another phase II/III RCT, is investigating the efficacy of ketamine as a first-line agent for refractory status epilepticus. Both the trials are in the recruitment stage.

**Exacerbation of severe bronchial asthma**

Evidence shows that inhalational ketamine is effective for the treatment of severe exacerbations of asthma.\cite{66} It leads to improved outcomes and a reduction in the need for mechanical ventilation. It inhibits inflammatory cascade, reduces inflammatory markers, and causes bronchodilation. Systemic effects like anxiolysis and decrease in mechanical work of breathing also contribute to this effect.\cite{66}

In an RCT, i.v. ketamine in 0.4–0.5 mg/kg doses, followed by an infusion for 30 minutes produced a significant reduction in the peak expiratory flow rate (PEFR) among patients with mild-to-moderate bronchial asthma.\cite{67} Ketamine has shown comparable efficacy to aminophylline in children with bronchial asthma poorly responding to standard therapy.\cite{68}

A pilot study (NCT03338205)\cite{69} is ongoing to assess the safety and utility of ketamine as adjuvant therapy in pediatric patients with acute status asthmaticus not responding to standard therapy.
Role as an immunomodulator
Ketamine has an immunomodulatory role as it interferes with the production of early mediators of immunity, reduces the proinflammatory influences, and prevents the extension of local inflammation. Its anti-inflammatory effect is thought to be due to inhibition of high mobility group box 1 (HMGB1) induced activation of endothelial cells. It also increases mTOR signalling and subsequently suppresses autophagy and helps in amelioration of inflammation in ischaemia/reperfusion in the brain and in airway allergy. However, ketamine also increases the levels of cytokines IL–6 and IL–1β in mice hippocampus and has potential to cause neuroinflammation leading to neurodegeneration.

CHALLENGES IN REPURPOSING KETAMINE: SAFETY, CAUTIONS, AND WARNINGS

The side effects of ketamine are dose-related. Psychotomimetic phenomena like euphoria, dysphoria, psychomotor retardation, hallucinations, vivid dreams, and nightmares are common adverse effects. Subanesthetic doses of ketamine can cause impairment of attention, memory, and judgement. At higher anesthetic doses, tonic-clonic movements are very common (>10%). Ketamine, in induction doses, can increase heart rate, blood pressure, and cardiac output and increases myocardial oxygen demand, making it unsuitable for the patients at risk of myocardial ischaemia.

Ketamine should be used cautiously in patients with a history of psychiatric disorders, cerebrovascular accidents, epilepsy, glaucoma, hypertension, or ischaemic heart disease.

Following toxicities are the concerns with long term use of ketamine and pose challenges in repurposing ketamine.

Neurotoxicity
Ketamine causes potent cerebral stimulation, especially in patients of seizure disorders, in whom it activates subcortical seizure activity. It triggers clinical or electroencephalogram (EEG) seizure activity at doses >2 mg/kg intravenously. It can cause subpial vacuolar myelopathy; focal lymphocytic vasculitis in medullary tissue, nerves, and leptomeninges of the spinal cord; and gliosis when administered intrathecally. It increases cerebral blood flow and intracranial pressure; this raises the alarm regarding its use in patients with compromised intracranial compliance. However, the cerebral perfusion is not adversely affected. It should be avoided only in patients with structural obstruction to cerebral blood flow.

Ketamine produced a dose- and duration-dependent increase in the levels of proinflammatory cytokines like IL–6 and IL–1β in the mice hippocampus, and this suggested that ketamine may lead to neurodegeneration. An increased expression of Toll-like receptor–4 (TLR–4) by ketamine causes the subsequent increase in the proinflammatory cytokines.

Cognitive impairment
Ketamine administration in healthy volunteers may produce central nervous system depression and/or intoxication, perceptual alterations, referential ideas or delusion, and negative symptoms such as mild-to-moderate alogia and increased latency of responding. In a preclinical study, it was observed that a single subanesthetic dose of ketamine might cause protein damage and lipid peroxidation in the hippocampus. This consequently affects the memory acquisition and retrieval. However, no reduction in memory consolidation was observed.

Urinary tract toxicity
Evidence suggests that long term use of ketamine is associated with the urinary tract toxicity. It can cause symptoms such as frequency and urgency of micturition, urge incontinence, dysuria, and irritation. These generally settle after a few weeks of stopping ketamine. Findings such as bladder instability, detrusor overactivity, interstitial cystitis, vesicoureteric reflux, hydronephrosis, papillary necrosis, and renal impairment are observed during urinary tract investigations. Irreversible damage may lead to renal failure. The mechanism behind this is still not clear; however, in vitro studies have revealed that there was a direct interaction between ketamine and urinary bladder.

Abuse potential of ketamine
Ketamine is generally abused as a recreational drug and carries a strong reinforcing effect. It is mostly used intranasally, which produces rapid effects, and there is a need to tightly regulate its availability in the market. The primary psychological effects of ketamine are anesthesia and sedation. When abused, it produces relaxation at low doses and a dream-like state at high doses. Acute use produces ethanol-like effects, and chronic use produces positive and negative symptoms of schizophrenia. It is hypothesized that, increased dopamine release due to ketamine-induced blockade of NMDA receptors on GABA neurons in the reticular nucleus of the thalamus is the basic mechanism of its abuse. A single subanesthetic dose of ketamine has
have been shown to increase the level of dopamine in the prefrontal cortex of rats.[86]

CONCLUSION

Ketamine appears to hold a promising repurposing potential for the treatment of various conditions like major depression, generalized and social anxiety disorders, refractory status epilepticus, substance use disorders, and bronchial asthma exacerbations. In addition, esketamine has been recently approved for TRD. However, given its recreational effects, abuse potential, and potential safety concerns, long term use of ketamine may pose a problem and should be carefully watched for. There is a need to do tremendous research and generate a high level of evidence to ascertain its efficacy and safety for these indications.

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