Review Article

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}

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channels (BK channels). Also, it causes activation of μ and δ opioid, α-amino-3-hydroxy-5-methyl-4-isoxazo lepropionic acid, (AMPA) and γ –aminobutyric acid A ($GABA_A$) receptors.[3]

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.

Anesthesia

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.[5] 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]

Analgesia

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.[8] 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	Lauretti *et al*., 1999[10] Finkell *et al*., 2007[11]
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[23] Philips *et al*., 2019[24] Zheng *et al*., 2019[25] Singh *et al*., 2016[32]* Daly *et al*., 2017[33]*
Cocaine Use Disorder	Improved prefrontal cortex glutamate homeostasis causing synaptic improvements	Dakwar *et al*., 2017[38]
Opioid Use Disorder	Improved prefrontal cortex glutamate homeostasis, causing synaptic improvements	Krupitsky *et al*., 2002[40] Krupitsky *et al*., 2007[41] Jovaisa *et al*., 2006[42]
Alcohol Use Disorder	Improved prefrontal cortex glutamate homeostasis, causing synaptic improvements	Wong *et al*., 2015[45]
Suicidal Ideation	Increased signaling via mTOR, BDNF and GSK-3 pathways	Canuso *et al*., 2018[48] Grunebaum *et al*., 2018[49] Grunebaum *et al*., 2017[50] Fan *et al*., 2017[28]
Anxiety Disorders (SAD, GAD)	Increased BDNF signaling in hippocampus	Taylor *et al*., 2018[55] Glue *et al*., 2018[56]
Refractory Status Epilepticus	NMDA antagonism and reduction in NMDA induced neurotoxicity	Rosati *et al*., 2012[62] Ilvento *et al*., 2015[63]
Bronchial Asthma	Inhibition of inflammatory cascade, reduction in markers of inflammation and bronchodilatation	Esmailian *et al*., 2018[67] Tiwari *et al*., 2016[68]

*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 – Tropomyosin-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 (P13K)-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.[44] Ketamine reduced the requirement of benzodiazepines when used as an adjunct to them in the management of alcohol withdrawal symptoms.[45] Two Phase-2, placebo-controlled RCTs, NCT02649231 and NCT02461927, evaluating the efficacy of ketamine in alcohol use disorder are presently recruiting participants.[46,47]

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.[28,48-50] 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.[51] Another phase III RCT (NCT02418702), still in the prerecruitment phase, will evaluate the effect of ketamine on suicidal thinking of military persons.[52]

Anxiety disorders

The anxiolytic effects of ketamine in patients of major depression have been elucidated.[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.[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.[56] Mechanism of its antianxiety 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.[56,57]

A phase IV, midazolam controlled clinical trial (NCT02579928)[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)[57] 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).[59,60] Evidence also suggests that ketamine, at usual doses, has an epileptogenic potential and should be avoided in patients with epilepsy.[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.[62] However, large scale controlled trials are required to substantiate these findings.[62] 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.[63]

A phase III RCT (NCT02431663)[64] has been planned to evaluate the efficacy of intravenous administration of ketamine in children with RCSE while NCT03115489,[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.[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.[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.[67] Ketamine has shown comparable efficacy to aminophylline in children with bronchial asthma poorly responding to standard therapy.[68]

A pilot study (NCT03338205)[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.[6] Its antiinflammatory effect is thought to be due to inhibition of high mobility group box 1 (HMGB1) induced activation of endothelial cells.[70] 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.[71] However, ketamine also increases the levels of cytokines IL–6 and IL–1beta in mice hippocampus and has potential to cause neuroinflammation leading to neurodegeneration.[72]

CHALLENGES IN REPURPOSING KETAMINE: SAFETY, CAUTIONS, AND WARNINGS

The side effects of ketamine are dose-related.[2] Psychotomimetic phenomena like euphoria, dysphoria, psychomotor retardation, hallucinations, vivid dreams, and nightmares are common adverse effects.[73] Subanesthetic doses of ketamine can cause impairment of attention, memory, and judgement.[2] At higher anesthetic doses, tonic-clonic movements are very common (>10%).[2] 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.[74]

Ketamine should be used cautiously in patients with a history of psychiatric disorders, cerebrovascular accidents, epilepsy, glaucoma, hypertension, or ischaemic heart disease.[2]

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.[75] It triggers clinical or electroencephalogram (EEG) seizure activity at doses >2 mg/kg intravenously.[75] It can cause subpial vacuolar myelopathy; focal lymphocytic vasculitis in medullary tissue, nerves, and leptomeninges of the spinal cord; and gliosis when administered intrathecally.[76,77] 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.[78]

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.[72] An increased expression of Toll-like receptor–4 (TLR–4) by ketamine causes the subsequent increase in the proinflammatory cytokines.[72]

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.[79] In a preclinical study, it was observed that a single subanesthetic dose of ketamine might cause protein damage and lipid peroxidation in the hippocampus.[80] This consequently affects the memory acquisition and retrieval. However, no reduction in memory consolidation was observed.[80]

Urinary tract toxicity

Evidence suggests that long term use of ketamine is associated with the urinary tract toxicity.[81] 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.[82,83] 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.[84]

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.[85] 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.[85] A single subanesthetic dose of ketamine has

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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REFERENCES

1. Domino EF. History and pharmacology of PCP and PCP –related analogs. J Psychedelic Drugs 1980;12:223-7.
2. Quibell R, Prommer EE, Mihalyo M, Twycross R, Wilcock A. Ketamine. J Pain Symptom Manage 2011;41:640-9.
3. Li L, Vlisides PE. Ketamine: 50 years of modulating the mind. Front Hum Neurosci 2016;10:612.
4. Chong CR, Sullivan DJNew uses for old drugs. Nature 2007;448:645-6.
5. Trimmel H, Helbok R, Staudinger T, Jaksch W, Messerer B, Schohl H, *et al*. S (+) –ketamine: Current trends in emergency and intensive care medicine. Wien Klin Wochensch 2018;130:356-66.
6. Gao M, Rejaei D, Liu H. Ketamine use in current clinical practice. Acta Pharmacol Sin 2016;37:865-72.
7. Tsze DS, Steele DW, Machan JT, Akhlaghi F, Linakis JG. Intranasal ketamine for procedural sedation in pediatric laceration repair: A preliminary report. Pediatr Emerg Care 2012;28:767-70.
8. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P. Ketamine and ketamine metabolite pharmacology: Insights into therapeutic mechanisms. Pharmacol Rev 2018;70:621-60.
9. Gottlieb M, Ryan KW, Binkley C. Is low dose ketamine an effective alternative to opioids for the treatment of acute pain in the emergency department? Ann Emerg Med 2018;72:133-4.
10. Lauretti GR, Lima I, Reis MP, Prado WA, Pereira NL. Oral ketamine and transdermal nitroglycerine as analgesic adjuvants to oral morphine therapy for cancer pain management. Anaesthesiology 1999,90:1528-33.
11. Finkell JC, Pestieau SR, Quezado ZM. Ketamine as an adjuvant for the treatment of cancer pain in children and adolescents. J Pain 2007;8:515-21.
12. Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev 2017;6:CD003351.
13. Bredlau AL, Thakur R, Korones DN, Dworkin RH. Ketamine for pain in children and adults with cancer: A systemic review and synthesis of literature. Pain Med 2013;14:1505-17.
14. Intranasal (NAS) ketamine for pain (NCT03146806). Available from: https://clinicaltrials.gov/ct2/show/NCT03146806. [Last accessed on 2019 Apr 22].
15. Continuous IntraVenous Infusion of Ketamine in Terminally Ill Cancer Patients (CIVIK) (NCT03362073). Available from: https://clinicaltrials.gov/ct2/show/NCT03362073. [Last accessed on 2019 Apr 22].
16. Rigo FK, Trevisan G, Godoy MC, Rossato MF, Dalmolin GD, Silva MA, *et al*. Management of neuropathic pain with methadone combined with ketamine: A randomized, double blind, active controlled trial. Pain Physician 2017;20:207-15.
17. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: A double blind placebo controlled study. Pain 2009;147:107-15.
18. Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous MS, Marinus J, Sarton EY, *et al*. Ketamine produces effect and long term pain relief in patients with complex regional pain syndrome. Pain 2009;145:304-11.
19. Mion G, Villevielle T. Ketamine pharmacology: An update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther 2013;19:370-80.
20. Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS. Ketamine: A Paradigm shift for depression research and treatment. Neuron 2019;101:774-8.
21. Ibrahim L, Diazgranados N, Franco –Chaves J, Brutsche N, Henter ID, Kronstein P, *et al*. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vsadd –on riluzole: Results from a 4 –week, double –blind, placebo controlled study. Neuropsychopharmacology 2012;37:1526-33.
22. Mathew SJ, Murrough JW, Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment resistant depression: Apilot randomized, placebo –controlled continuation trial. Int J Neuropsychopharmacol 2010;13:71-82.
23. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, *et al*. Antidepressant efficacy of ketamine in treatment –resistant major depression: A two –site, randomized, parallel –arm, midazolam controlled clinical trial. Am J Psychiatry 2013;170:1134-42.
24. Phillips JL, Norris S, Talbot J, Birmingham M, Hatchard T, Ortiz A, *et al*. Single, repeated and maintenance ketamine infusions for treatment –resistant depression: A randomized controlled trial. Am J Psychiatry 2019;176:401-9.
25. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ. Investigation of medical effects of multiple ketamine infusions on patients with major depressive disorder. J Psychopharmacol 2019;33:494-501.
26. Bryant KA, Altinay M, Finnegan N, Cromer K, Dale RM. Effects of repeated intravenous ketamine in treatmetresistant geriatric depression: A case series. J Clin Psychopharmacol 2019;39:158-61.
27. DeWilde KE, Levitch CF, Murrough JW, Mathew SJ, Iosifescu D. The promise of ketamine for treatment –resistant depression: Current evidence and future directions. Ann N Y Acad Sci 2015;1345:47-58.
28. Fan W, Yang H, Sun Y, Zhang J, Li G, Zheng Y, *et al*. Ketamine rapidly relieves acute suicidal ideation in cancer patients: Arandomized controlled clinical trial. Oncotarget 2017;8:2356-60.
29. Evaluation of Schemes of Administration of Intravenous

Ketamine in Depression (NCT03742557). Available from: https://clinicaltrials.gov/ct2/show/NCT03742557. [Last accessed on 2019 Apr 24].
30. Low Dose Intravenous Ketamine in Treatment Resistant Depression Patients (NCT02935595). Available from: https://clinicaltrials.gov/ct2/show/NCT02935595. [Last accessed on 2019 Apr 25].
31. FDA approves new nasal spray medication for treatment –resistant depression; available only at a certified doctor's office or clinic. Available from: https://www.fda.gov/news –events/press –announcements/fda –approves –new –nasal –spray –medication –treatment –resistant –depression –available –only –certified. [Last accessed on 2019 Apr 24].
32. Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, *et al*. Intravenous esketamine in adult treatment –resistant depression: Adouble –blind, double –randomization, placebo –controlled study. Biol Psychiatry 2016;80:424-31.
33. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton. Efficacy and safety of intranasal esketamineadjunctive to oral antidepressant therapy in treatment resistant depression: A randomized controlled clinical trial. JAMA Psychiatry 2018;75:139-48.
34. Correia –Melo FS, Leal GC, Carvalho MS, Jesus –Nunes AP, Ferreira CBN, Vieira F, *et al*. Comparative study of esketamine and racemic ketamine in treatment –resistant depression: Protocol for a non –inferiority clinical trial. Medicine 2018;97:e12414.
35. Molero P, Ramos –Quiroga JA, Martin –Santos R, Calvo –Sanchez E, Gutierrez –Rojas L. Antidepressant efficacy and tolerability of ketamine and esketamine: A critical review. CNS Drugs 2018;32:411-20.
36. Morrison RL, Fedgchin M, Singh J, Van Gerven J, Zuiker R, Lim KS, *et al*. Effect of intranasal esketamine on cognitive functioning in healthy participants: Arandomized double –blind, placebo controlled study. Psychopharmacology 2018;235:1107-19.
37. Dakwar E, Levin F, Foltin RW, Nunes EV, Hart CL. The effects of subanaesthetic ketamine infusions on motivation to quit and cue induced craving in cocaine dependent research volunteers. Biol Psychiatry 2014;76:40-6.
38. Dakwar E, Hart CL, Levin FR, Nunes EV, Foltin RW. Cocaine self administration disrupted by the N –methyl –D –aspartate receptor antagonist ketamine: Arandomized, cross over trial. Mol Psychiatry 2017;22:76-81.
39. Glutamatergic modulation to facilitate the behavioral treatment of cocaine use disorders (NCT03344419) Available from: https://clinicaltrials.gov/ct2/show/NCT03344419. [Last accessed on 2019 Apr 24].
40. Krupitsky E, Burakov A, Romanova T, Dunaevsky I, Strassman R, Grinenko A. Ketamine psychotherapy for heroin addiction: Immediate effects and two –year follow up. J SubstAbus Treat 2002;23:273-83.
41. Krupitsky E, Burakov A, Dunaevsky I, Romanova TN, Slavina TY, Grinenko A. Single versus repeated sessions of ketamine –assisted psychotherapy for people with heroin dependence. J Psychoact Drugs 2007;39:13-9.
42. Jovaisa T, Laurinenas G, Vosylius S, Sipylaite J, Badaras R, Isvaskevicius J. Effects of ketamine on precipitated opiate withdrawal. Medicina2006;42:625-34.
43. Facilitating rapid Naltrexone initiation (NCT03345173). Available from: https://clinicaltrials.gov/ct2/show/NCT03345173. [Last accessed on 2019 Apr 24].
44. Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): Areview of the results of ten years of research. J Psychoact Drugs 1997;29:165-83.
45. Wong A, Benedict NJ, Armahizer MJ, Kane –Gill SL. Evaluation of adjunctive ketamine to benzodiazepines for the management of alcohol withdrawal syndrome. Ann Pharmacother 2015;49:14-9.
46. Ketamine for reduction of alcoholic relapse (KARE) (NCT02649231). Available from: https://clinicaltrials.gov/ct2/show/NCT02649231. [Last accessed on 2019 Apr 24].
47. Ketamine for the rapid treatment of major depressive disorder and alcohol use disorder (NCT02461927). Available from: https://clinicaltrials.gov/ct2/show/NCT02461927. [Last accessed on 2019 Apr 25].
48. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, *et al*. efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: Results of a double –blind, randomized, placebo –controlled study. Am J Psychiatry 2018;175:620-30.
49. Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, *et al*. Ketamine for rapid reduction of suicidal thoughts in major depression: Amidazolam –controlled randomized clinical trial. Am J Psychiatry 2018;175:327-35.
50. Grunebaum MF, Ellis SP, Keilp JG, Moitra VK, Cooper TB, Marver JE, *et al*. Ketamine versus midazolam in bipolar depression with suicidalthoughts: A pilot midazolam –controlled randomized clinical trial. Bipolar Disord 2017;19:176-83.
51. Ketamine for Acute Suicidal Ideation in the Emergency Department: Randomized Controlled Trial (LDK –SI) (NCT01892995). Available from: https://clinicaltrials.gov/ct2/show/NCT01892995. [Last accessed on 2019 Apr 25].
52. A study to decrease suicidal thinking using ketamine (NCT02418702). Available from: https://clinicaltrials.gov/ct2/show/NCT02418702. [Last accessed on 2019 Apr 25].
53. Salvadore G, Cornwell BR, Colon –Rosario V, Coppola R, Grillon C, Zarate CA, *et al*. Increased anterior cingulate cortical activity in response to fearful faces: Aneurophysiological biomarker that predicts rapid antidepressant response toketamine. Biol Psychiatry 2009;65:289-95.
54. Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, *et al*. A randomized trial of an N –methyl –D –aspartate antagonist in treatment –resistant major depression. Arch Gen Psychiatry 2006;63:856-64.
55. Taylor JH, Landeros –Weisenberger A, Coughlin C, Mulqueen J, Johnson JA, Gabriel D. Ketamine for social anxiety disorder: A randomized, placebo controlled cross over trial. Neuropsychopharmacology 2018;43:325-33.
56. Glue P, Neehoff SM, Medlicott NJ, Gray A, Kibby G, McNaughton N. Safety and efficacy of maintenance ketamine in patients with treatment –refractory generalized anxiety and social anxiety disorders. J Psychopharmacol 2018;32:663-7.
57. Intranasal ketamine for anxiolysis in pediatric emergency department patients (NCT03043430). Available from: https://clinicaltrials.gov/ct2/show/NCT03043430. [Last accessed on 2019 Apr 25].
58. Ketamine infusion for adolescent depression and anxiety (NCT02579928). Available from: https://clinicaltrials.gov/ct2/show/NCT02579928. [Last accessed on 2019 Apr 25].
59. Fang Y, Wang X. Ketamine for the treatment of refractory status epilepticus. Seizure 2015;30:14-20.
60. Gaspard N, Foreman B, Judd LM, Brenton JN, Nathan BR, McCoy BM, *et al*. Intravenous ketamine for the treatment of refractory status epilepticus: Aretrospective multicenter study. Epilepsia 2013;54:1498-503.
61. Maranhao MV, Gomes EA, de Carvalho PE. Epilepsy and anaesthesia. Rev Bras Anestesiol 2011;61:232-54.
62. Rosati L, L'Erario M, Ilvento L, Cecchi C, Pisano T, Mirabie L,

et al. Efficacy and safety of ketamine in refractory status epilepticus in children. Neurology 2012;11;79:2355-8.
63. Ilvento L, Rosati A, Marini C, L'Erario M, Mirabile L, Guerrini R. Ketamine in refractory convulsive status epilepticus in children avoids endotracheal intubation. Epilepsy Behav 2015;49:343-6.
64. Ketamine in Refractory Convulsive Status Epilepticus (KETASER01) (NCT02431663). Available from: https://clinicaltrials.gov/ct2/show/NCT02431663. [Last accessed on 2019 Apr 25].
65. Efficacy of ketamine infusion compared with traditional anti –epileptic agents in Refractory Status Epilepticus (NCT03115489). Available from: https://clinicaltrials.gov/ct2/show/NCT03115489. [Last accessed on 2019 Apr 25].
66. Elkoundi A, Bentalha A, El Koraichi A, El Kettani SE. Nebulized ketamine to avoid mechanical ventilation in a pediatric patient with severe asthma exacerbation: Case report. Am J Emerg Med 2018;36:734.e3-734.e4.
67. Esmailian M, Koushkian Esfahani M, Heydari F. The effect of low –dose ketamine in treating acute asthma attack; a randomized clinical trial. Emerg (Tehran) 2018;6:e21.
68. Tiwari A, Guglani V, Jat KR. Ketamine versus aminophylline for acute asthma in children. Ann Thorac Med 2016;11:283-8.
69. The role of ketamine as an adjuvant therapy for children with acute status asthmaticus (NCT03338205). Available from: https://clinicaltrials.gov/ct2/show/NCT03338205. [Last accessed on 2019 Apr 25].
70. Palumbo R, Sampaolesi M, De Marchis F, Tolnorenzi F, Colombetti S, Mondino A. Extracellular HMGB1, a signal of tissue damage induces mesangioblast proliferation. J Cell Biol2004;164:441-9.
71. Zou H, Wang LX, Wang M, Cheng C, Li S, Shen O, *et al*. MTOR –mediated allergy is involved in the protective effect of ketamine on allergic airway inflammation. J Immunol Res 2019;2019:5879714.
72. Li Y, Shen R, Wen G, Ding R, Du A, Zhou J, *et al*. Effects of ketamine on levels of inflammatory cytokines IL –6, IL –1beta, and TNF –alpha in the hippocampus of mice following acute or chronic administration. Front Pharmacol2017;8:139.
73. Bell RF, Kalso EA. Ketamine for pain management. Pain Rep 2018;3:e674.
74. Patel HH, Pearn ML, Patel PM, Roth DM. General anaesthetics and therapeutic gases. In: Brunton L, Hilal –Dandan R, Knollman BC, editors. The Pharmacological Basis of Therapeutics. 13th ed.. Mc Graw Hill: USA; 2018. p. 387-404.
75. Modica CA, Tempelhoff R, White PF. Pro – and Anticonvulsant effects of anaesthetics (Part II). Anesth Analg 1990;70:433-44.
76. Karpinski N, Dunn J, Hansen L, Masliah E. Subpial vacuolar myelopathy after intrathecal ketamine: Report of a case. Pain1997;73:103-5.
77. Stotz M, Oehen HP, Gerber H. Histopathological findings after long term infusion of intrathecal ketamine for chronic pain: A case report. J Pain Symptom Manage 1999;18:223-38.
78. Green SM, Andolfatto G, Krauss BS. Ketamine and intracranial pressure: No contraindication except hydrocephalus. Ann Emerg Med 2015;65:52-4.
79. Pomarol –Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, Lee M, *et al*. Psychological effects of ketamine in healthy volunteers. Br J Psychiatry 2006;189:173-9.
80. Rosenbrock HD –CC, Kroker K, Rast G. Effect of specific nicotinic acetylcholine receptor agonists on hippocampal longterm potentiation. Alzheimer's Dement 2011;7:S116.
81. Wei YB, Yang JR, Yin Z, Guo Q, Liang BL, Zhou KQ. Genitourinary toxicity of ketamine. Hong Kong Med J 2013;19:341-8.
82. Chu PS, Ma WK, Wong SC, Chu RW, Cheng CH, Wong S, *et al*. The destruction of lower urinary tract by ketamine abuse: Anew syndrome? BJU Int 2008;102:1616-22.
83. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine associated ulcerative cystitis: A new clinical entity. Urology 2007;69:810-2.
84. Bell RF. Ketamine for chronic noncancer pain: Concerns regarding toxicity. CurrOpin Support Palliat Care 2012;6:183-7.
85. Liu Y, Lin D, Wu B, Zhou W. Ketamine abuse potential and use disorder. Brain Res Bull 2016;126:68-73.
86. Xu K, Lipsky RH. Repeated ketamine administration alters N –methyl –D –aspartic acid receptor subunit gene expression: Implication of genetic vulnerability for ketamine abuse and ketamine psychosis in humans. Exp Biol Med 2015;240:145-55.