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Review Article

CLINICAL PRACTICE

The diverse effects of ketamine, jack-of-all-trades: a narrative review

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Summary

Ketamine, an N-methyl-D-aspartic acid receptor antagonist that was first discovered in 1962, has become established in anaesthesia providing dose-dependent anaesthetic, sedative, and analgesic effects. Ketamine, however, also acts on a wide range of other cellular targets, resulting in interesting and diverse effects on both physiological and pathological processes. Potential beneficial properties of ketamine include cardiovascular stability for patients undergoing sedation or anaesthesia, analgesia in both acute and chronic pain, bronchodilation in severe refractory asthma, anti-inflammatory properties particularly in sepsis, tumour inhibition, and antidepressant properties with marked ability to reverse suicidal ideation. The reluctance to adopt ketamine into routine practice is likely attributable in part to the stigma and negative reputation associated with its perceived side-effects and potential for abuse. This review explores the diverse properties and therapeutic potentials of ketamine being investigated across different fields whilst also identifying areas for ongoing and future research. Given the diverse range of potential benefits and promising early work, ketamine should be the focus of ongoing research in multiple different specialty areas. This includes areas relevant to anaesthesia and perioperative medicine, such as acute and chronic pain management, ICU sedation, and even tumour suppression in those undergoing surgical resection of malignancies.

Keywords: anaesthesia; analgesia; anti-inflammatory properties; antidepressant effects; ketamine; sedation; tumour suppression; NMDA receptor antagonist

Editor's key points

- Ketamine, an NMDA receptor antagonist, is well known in anaesthesia for providing dose-dependent anaesthetic, sedative, and analgesic effects.
- This review presents and discusses the lesser-known effects of ketamine, such as bronchodilation, immune modulation, tumour inhibition, and antidepressant properties, highlighting its therapeutic potential across various contexts.
- Evidence supporting ketamine use in clinical practice is limited in some respects. Future work should focus on producing robust evidence for ketamine use in these contexts.

Ketamine is a water and lipid-soluble N-methyl-D-aspartic acid (NMDA) receptor antagonist that has been used since the 1970s to provide cataleptic, amnesic, analgesic, and dose-dependent anaesthetic effects.[1]

Ketamine was discovered in 1962 by Parke-Davis (now Pfizer Inc.) during research into the psychotropic and anaesthetic effects of phencyclidine (PCP). Ketamine, identified as a PCP derivative with short-acting anaesthetic effects and a strong safety profile, gained Food and Drug Administration (FDA) approval in 1970[2] and has been listed on the WHO Model List of Essential Medicines as an intravenous anaesthetic since 1984, when it was first added.[3]

Ketamine has gained popularity as an anaesthetic agent owing to its favourable cardiovascular effects in haemodynamically compromised patients. However, ketamine also has

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more diverse effects including bronchodilation in asthma, anti-inflammatory effects in sepsis, neuroprotective properties, tumour inhibition, and prolonged antidepressant effects, which are discussed in more detail in this review.

Structure and mechanism of action

Ketamine comprises two asymmetrical enantiomers: the S(+) isomer and R(−) isomer. Both isomers have similar pharmacokinetics, although S-ketamine demonstrates higher affinity for the NMDA receptor resulting in greater anaesthetic and analgesic properties but with fewer psychomimetic side-effects. Emergence from anaesthesia is faster with S-ketamine as metabolism is slower in racemic and R-ketamine compared with S-ketamine alone (Table 1).[1,4,5]

Although the predominantly described mechanism of action is non-competitive antagonism of the NMDA and glutamate receptors, ketamine also targets dopaminergic, serotonergic, adrenergic, cholinergic, opioid, and sigma receptors.[1,6] In addition, ketamine acts on serotonin, norepinephrine, and dopamine reuptake transporters and on various ion channels including voltage-gated sodium channels and hyperpolarisation-activated cyclic nucleotide-gated channels (Table 2).[7–9]

The beneficial cardiovascular effects of ketamine are attributed to sympathetic stimulation through endogenous catecholamine release, vagal nerve inhibition, and preventing norepinephrine reuptake. The cardiovascular effects of ketamine are, however, more complicated than this; ketamine has a directly negative inotropic effect on the heart, but in patients with an intact autonomic nervous system, this is usually outweighed by ketamine preventing the reuptake of endogenous epinephrine and norepinephrine.[6,10,11]

Ketamine increases coronary perfusion and coronary oxygen supply whilst increasing myocardial oxygen demand through increasing heart rate and contractility.[12] There is also an associated increase in pulmonary artery pressure and pulmonary vascular resistance and therefore right ventricular stroke work.[13]

Table 1 Pharmacokinetic differences between S-ketamine and R-ketamine.[1,4,5]

	S-Ketamine	R-Ketamine
Affinity for NMDA receptor	Higher affinity (two to four times)	Lower affinity
Onset of action	Faster onset	Slower onset
Elimination half-life	Faster elimination	Slower elimination
Metabolism	Slightly faster metabolism (CYP450)	Slightly slower metabolism (CYP450)
Anaesthetic effects	More potent	Less potent
Psychotropic effects	Fewer dissociative side-effects	Increased dissociative side-effects
Analgesic effects	Longer duration	Shorter duration
Antidepressant effects	Less potent and shorter duration	More potent and longer duration

Table 2 Ketamine receptor targets and actions.[9]

Receptor target	Action
Glutamate receptor ionotropic, NMDA 3A	Antagonist
5-Hydroxytryptamine receptor 3A	Potentiator
Neuronal acetylcholine receptor subunit alpha-7	Antagonist
Cholinesterase	Inhibitor
Nitric oxide synthase, brain	Inhibitor
Neurokinin 1 receptor	Antagonist
Dopamine D2 receptor	Agonist/partial agonist
Delta-type opioid receptor	Binds
Sodium-dependent norepinephrine transporter	Inhibitor
Kappa-type opioid receptor	Agonist
Mu-type opioid receptor	Binder
Muscarinic acetylcholine receptor	Binder
5-Hydroxytryptamine receptor 2	Antagonist
Voltage-gated sodium channels	Antagonist
Hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels	Antagonist

The baroreceptor response to a decrease in blood pressure, which is attenuated with anaesthetic agents such as barbiturates, is preserved with ketamine.[14]

Route of administration

Ketamine can be administered via intravenous, intramuscular, intraosseous, subcutaneous, intranasal, oral, sublingual, epidural, and intrarectal routes.[15,16]

Intravenous administration provides rapid maximum plasma concentrations (2–4 min),[17] and being highly lipid soluble, ketamine rapidly crosses the blood–brain barrier, reaching therapeutic levels quickly (effector-site equilibration half-time of approximately 2 min[18]), and has a large volume of distribution (2–5 L kg^{-1}).[4]

Intramuscular administration also has fast peak plasma concentrations (5–30 min) and a high bioavailability (93%).[19]

Metabolism

Ketamine undergoes cytochrome P450-mediated N-demethylation and hydroxylation in the liver, forming (R,S)-norketamine, its primary metabolite. Norketamine is an active metabolite with approximately 20–30% of the anaesthetic and analgesic properties of ketamine but with a longer elimination time compared with ketamine, resulting in sustained clinical effects and decreasing ketamine requirements over time during continuous infusion.[1,4,20]

Ketamine has a high clearance rate, equivalent to hepatic blood flow, and a short elimination half-life (2–4 h), being predominantly eliminated in bile and urine as hydroxylated derivatives of ketamine (80%), dehydroxynorketamine (16.2%), norketamine (1.6%), and unchanged ketamine (2.3%).[1,21]

Ketamine clearance is largely unaffected by renal impairment, with plasma concentrations not significantly varying in acute renal failure compared with normal renal function. Norketamine levels are, however, significantly higher in renal impairment.[22] Estimates of ketamine removal during

continuous haemodialysis or haemofiltration range from 0.5% to 10%.[22,23]

Established uses for ketamine

General anaesthesia

Ketamine is a *dissociative anaesthetic*, named so because of the feeling of disconnect from the physical world that recipients experience and can be used for both the induction and maintenance of anaesthesia. A bolus dose of 0.5–2 mg kg^{-1} given intravenously provides dissociative anaesthesia after 2–4 min. This dissociative state can be maintained with a continuous infusion of 10–45 μg kg^{-1} min^{-1}.[24,25]

The exact mechanism through which ketamine provides these effects remains disputed. Although non-competitive NMDA blockade is often cited, in reality, it is likely a combination of actions, as more potent NMDA receptor antagonists do not demonstrate more potent dissociative properties.[26]

Although robust clinical trial data for hospital use are limited, ketamine is recognised for providing haemodynamic stability[6,11,27] and is associated with significantly less adrenal suppression than etomidate,[28,29] which previously had been the recommended agent in hypotensive patients. These properties have led to increasing use for induction of anaesthesia in both military and civilian trauma anaesthesia, for induction of anaesthesia in the emergency department, and for hypotensive patients requiring emergency surgery.[27,30–34]

Ketamine is also used successfully in obstetric anaesthesia and is one of the few drugs approved for induction of anaesthesia for Caesarean section.[6] It provides effective anaesthesia without significant neonatal respiratory depression and maintains normal neonatal oxygenation at appropriate doses (1–1.5 mg kg^{-1}).[35] In obstetric cases, ketamine offers better intubating conditions than thiopental, with similar onset and recovery times.[36]

Procedural sedation

The use of ketamine for procedural sedation in the paediatric population is well established and considered safe and effective.[37,38]

In recent years, it has been increasingly used for adult procedural sedation because of its unique ability to provide sedation and analgesia while maintaining haemodynamics and respiratory reflexes.[39,40]

Intravenous doses of 0.2–0.8 mg kg^{-1} typically achieve the desired sedation within 1 min, lasting 5–10 min.[38]

One limitation to the use of ketamine for short procedural sedation is the unwanted psychomotor side-effects; however, co-administering small doses of propofol or benzodiazepines has been found to be effective at reducing these.[41,42]

Spinal and regional anaesthesia

Ketamine provides marked analgesic effects when administered either alone or in combination with local anaesthetics as part of a spinal anaesthesia.[43,44]

A recent meta-analysis conducted by Xiang and colleagues[45] in 2024 found that ketamine combined with local anaesthetic provided prolonged duration of analgesia, particularly when used for peripheral nerve blocks, compared with use of local anaesthetics alone.[45]

Ketamine in this application has the additional benefits of few to no life-threatening adverse effects of accidental intravenous or intrathecal administration.

Widespread use of spinal ketamine has been limited by concerns over neurotoxicity, particularly in neonates, although studies on this have shown mixed or contradictory results.[46–49] Concerns regarding ketamine neurotoxicity and potential neuroprotective properties are discussed later.

Use in pre-hospital, military, and disaster medicine

Many services, both in the UK and internationally, use ketamine for both sedation and anaesthesia in a pre-hospital context owing to its beneficial effects, wide safety margin, multiple routes of administration, and ease of storage and transport. In addition, it has become a preferred anaesthetic in resource-limited environments.[32,33,50,51]

In 2002, Bonanno[50] reported that ketamine with a benzodiazepine provided safe and effective general anaesthesia during the civil war in Somalia. Following this, an Australian medical team reported using ketamine anaesthetics to perform 120 surgical procedures in austere conditions following the Boxing Day tsunami in Indonesia in 2004.[52] Mulvey and colleagues[51] also published their experiences of using ketamine to facilitate emergency surgery for victims of the 2005 Kashmir earthquake. Both reported ketamine as safe and effective in a resource-constrained environment, with a low incidence of reported major adverse events.

More recently, the pre-hospital use of ketamine received global attention after 13 people, 12 of whom were children, were rescued from a flooded cave system in Thailand in 2018.[53] The rescuer, an Australian anaesthetic consultant and cave diving expert, successfully used ketamine to provide anaesthesia to the individuals whilst avoiding the need for tracheal intubation and avoiding haemodynamic or respiratory compromise.

In the UK, there are fortunately few natural disasters resulting in the need for surgical procedures to be performed in austere environments. However, pre-hospital medicine has become a well-established practice, with ketamine being a useful agent for pre-hospital practitioners.

For example, in 2004, Porter[54] published a case series of 32 pre-hospital adult and paediatric trauma patients treated by the British Association of Immediate Care Scheme (BASICS). Porter[54] described ketamine as safe and effective for analgesia and anaesthesia in a mixed cohort of pre-hospital trauma patients, with no significant adverse airway effects and maintained blood pressure in patients with hypotension.

Other European countries have also adopted the pre-hospital use of ketamine; in a 2020 survey of members of a Swiss-based alpine helicopter rescue service, 100% of respondents reported ketamine to be safe and useful, and 62% even described ketamine as 'irreplaceable'. Neuropsychiatric side-effects were rare, and patient experiences were generally positive.[55]

Ketamine as an analgesic

Ketamine has been used in the treatment of both acute and chronic pain at doses that either use light sedative effects or at entirely subanaesthetic doses.

Ketamine provides analgesic effects similar to those of both morphine and fentanyl but without the pronounced respiratory depression associated with opiate and opioid medications.[56,57] Ketamine can provide enough analgesia for painful fracture manipulation, burns, and even

traumatic amputations whilst avoiding airway reflex suppression, respiratory depression, or haemodynamic compromise.[50,58,59]

The principal analgesic mechanism is most likely through NMDA antagonism: NMDA receptors are located throughout the central nervous system and are key in the transmission of central pain signals.[60,61]

Binding of ketamine to the NMDA receptor reduces calcium-mediated intracellular signalling and decreases channel opening duration and frequency whilst independently inhibiting pain, mediators such as neuronal nitric oxide synthase.[62–64]

Noxious stimulation of the NMDA receptor results in downregulation of opioid receptors and a dampened response from remaining opioid receptors, resulting in reduced opioid efficacy (tolerance) and hyperalgesia. By blocking the NMDA receptors, ketamine can prevent or reduce opioid tolerance and opioid-induced hyperalgesia and increase the efficacy of co-administered opioid medications.[65,66]

In chronic pain, NMDA receptors are upregulated, amplifying nociceptive signals. Ketamine is being considered for conditions such as complex regional pain syndrome and neuropathic pain.[67]

Given its side-effects and potential for abuse, the exact role of ketamine as an analgesic, particularly in the outpatient or community setting is still unclear. However, it is becoming increasingly recognised that ketamine plays an important role in multimodal analgesia, particularly for patients in the perioperative period.

The 2018 Cochrane review by Brinck and colleagues[68] demonstrates the utility of perioperative ketamine in reducing pain, opiate consumption, and postoperative nausea and vomiting across a wide range of operations and patient groups. Importantly, ketamine was not associated with a significant increase in psychomimetic side-effects compared with control.[68]

Ketamine is included in the National Institute for Health and Care Excellence (NICE) 2020 guidelines for managing moderate to severe pain in the perioperative period.[69]

More diverse properties and potential therapeutic uses for ketamine

Given that ketamine acts on a wide range of receptors and cellular processes, interest has grown in novel and alternative applications of ketamine in a variety of clinical settings.

Intensive care unit sedation

As described previously, ketamine use for induction and maintenance of anaesthesia is well established. However, it is not routinely used as a sedative for patients in the intensive care unit (ICU) undergoing mechanical ventilation.

A recent scoping review of ketamine use to facilitate mechanical ventilation found a lack of high-quality evidence supporting ketamine sedation in ICU.[70]

The review presents evidence to suggest that ketamine provides adequate sedation for patients undergoing mechanical ventilation and that some studies demonstrated additional benefits, such as improved haemodynamics and improved respiratory dynamics, with few or no adverse events including emergence reactions or increased intracranial pressure (ICP). The authors conclude that, currently, there is a lack of robust prospective evidence and that this should be a focus for future research.

Bronchodilation in asthma

Since the 1990s, it has been known that ketamine is able to mediate bronchodilation and prevent bronchoconstriction. A number of mechanisms for this have been described.

Experimental studies have found ketamine prevents NMDA-mediated airway constriction whilst also independently preventing histamine-induced tracheal constriction.[71]

Ketamine also inhibits L-type calcium channel-induced airway smooth muscle contraction, reduces acetylcholine-induced smooth muscle contraction by blocking parasympathetic vagal effects, and augments adrenaline-mediated bronchodilation.[72–74]

In addition, ketamine lessens the effect of endothelin-1, which induces bronchial smooth muscle constriction during severe asthma attacks[75,76] and reverses both tachykinin-induced[77] and histamine-induced[74] airway constriction in asthma. Ketamine has potent anti-inflammatory properties that suppress allergen-mediated airway hypersensitivity through reducing interleukin-4 and nitric oxide levels in animal asthma models.[78]

Despite this, studies investigating the use of asthma in clinical practice are currently lacking. This was highlighted by La Via and colleagues[79] in 2022, who concluded that the limited number of studies available and large heterogeneity prevented ketamine use in severe asthma from being recommended currently and that large, well-designed studies are required.

Ketamine use in psychiatry

Interest in using ketamine to treat numerous psychiatric conditions has gained traction over recent years. These include major depressive disorder (MDD), posttraumatic stress disorder (PTSD), and substance misuse.

In 2000, Berman and colleagues[80] published the first placebo-controlled trial of the antidepressant properties of ketamine in MDD, highlighting NMDA receptor modulation as a potential treatment mechanism. Since then, several meta-analyses have shown that ketamine provides rapid antidepressant effects in MDD and treatment-resistant MDD, with improvements lasting from days to weeks.[81–84] In 2024, Wang and colleagues[85] found ketamine also significantly reduced depression in the postnatal period.

Ketamine has been found to rapidly and significantly reverse suicidal ideation in depression, even when accounting for the severity of depression.[86,87]

The proposed antidepressant mechanism involves a transient surge in glutamate neurotransmission and subsequently prefrontal synaptic activity, possibly relating to the inhibition of Gamma-Aminobutyric Acid (GABA) interneurons, causing molecular and physiological changes that alleviate depression.[88]

Unlike traditional antidepressants, which can take several weeks or months to have the desired effect, the antidepressant effects of ketamine appear rapidly (within hours of administration). Although these effects outlast the usual therapeutic timescale of ketamine as a sedative or anaesthetic agent, repeated dosing may be required as the effects do not appear to be sustained indefinitely.[83,84]

Ketamine's antidepressant effects have also been studied in the perioperative setting. In 2016, Jiang and colleagues[89] demonstrated reduced PHQ-9 depression scores in elective surgical patients receiving ketamine compared with placebo ($P<0.01$). However, results on intraoperative ketamine have been mixed, with some showing benefits[90,91] and others finding none.[92,93]

In 2024, Shafique and colleagues[94] published a comprehensive review of the literature comparing S-ketamine and R-ketamine in depression. This review highlights the potential of R-ketamine to provide more potent and longer-lasting antidepressant effects compared with S-ketamine. Although there are promising animal and preclinical studies, the authors caution that overall data on R-ketamine in humans are limited.

Although there is no current consensus on the optimal isomer, route, or dose, in 2019, the US FDA licensed S-ketamine nasal spray alongside a conventional antidepressant for treatment-resistant depression.[95]

Given ketamine's use as an anaesthetic in trauma patients, researchers have investigated its effect on PTSD. Results are mixed; some found ketamine worsened re-experiencing, avoidance, and dissociation,[96] whereas others reported reduced PTSD symptoms.[97]

Mion and colleagues[98] in 2017 and Highland and colleagues[99] in 2020 noted that ketamine use was often linked to higher injury severity scores and thus a higher likelihood of PTSD. Mion and colleagues[98] found soldiers receiving ketamine had significantly higher injury severity scores ($P<0.001$) and PTSD prevalence ($P<0.001$), although ketamine was not identified as a risk factor in multivariate analysis. Highland and colleagues[99] found no difference in PTSD symptoms, suggesting ketamine at least does not worsen PTSD in patients with severe injuries.

In 2021, Feder and colleagues[100] conducted a small-scale randomised controlled trial of ketamine *vs* midazolam in chronic PTSD. Participants received six infusions for more than 2 weeks. Ketamine significantly improved PTSD symptoms 24 h after the first infusion, with an average effect lasting 27.5 days and a higher response rate compared with midazolam (67% *vs* 20%).

Studies have investigated the role of ketamine in the management of alcohol, cocaine, and opiate dependence or addiction, although these studies have been limited by small sample sizes and short duration of follow-up.[101]

Neuroprotection, neurotoxicity, and role in neurological disease

NMDA receptors play a key role in many central nervous system processes, including synaptic function, neuroplasticity, learning, and memory, with interesting implications for a variety of neurological diseases.[102]

Prolonged NMDA receptor activation, as seen in acute ischaemia or trauma, is linked to excitotoxicity and neuronal death. Conversely, NMDA receptor activation is crucial for neuronal survival, preventing apoptosis and age-related neurodegeneration. Underactivity may contribute to excitatory–inhibitory imbalances in conditions such as schizophrenia.[102–104]

Because of the varied, and often contrasting effects of NMDA receptor activity or inactivity, NMDA receptor antagonists, such as ketamine, exhibit both neuroprotective and neurotoxic properties.

Theories explaining these differences include receptor location (synaptic *vs* extrasynaptic), receptor subunit type, and duration or degree of activation or inhibition.[103,105,106]

In the 1980s, Olney and colleagues[107] identified intracellular vacuolation and mitochondrial lysis, or 'Olney's lesions', relating to high-dose NMDA antagonist exposure. Olney and colleagues[108] also noted that the immature human brain (from 6 months of gestation through to several years after birth) is especially vulnerable to apoptosis and neuronal death from NMDA antagonist or GABA-like exposure.

In 2014, Yan and Jiang[109] reviewed preclinical and clinical data, suggesting the neurotoxic and neuroprotective effects of ketamine may depend on dose, exposure frequency, and the presence or absence of noxious stimuli. This was highlighted by Brown and colleagues[110] in 2015, who found that lower doses (5 mg kg^{-1}) prevented apoptosis, whereas higher doses (20 mg kg^{-1}) induced apoptosis.

Despite the uncertainty over the neurotoxic or neuroprotective properties of NMDA antagonists, their benefits in specific diseases have been explored.

NMDA receptor-induced excitotoxicity after an acute stroke, ischaemic insult, or traumatic brain injury is thought to be a primary cause of acute neuronal death; calcium influx via activation of the NMDA receptor leads to an increase in neuronal nitric oxide synthase activity, and therefore nitric oxide, which triggers intracellular pathways resulting in neuronal cell death.[111] NMDA receptor antagonists, such as memantine or ketamine, have been shown to significantly reduce nitric oxide production and prevent neuronal cell death both *in vitro* and *in vivo*.[112–116] Ketamine has also been found to significantly reduce isoelectric spreading depolarisations after insults such as traumatic brain injury, subarachnoid haemorrhage, and malignant hemispheric stroke. These are responsible for damage and necrosis of functional neurons and are associated with poor neurological outcome.[117] Treatments using NMDA receptor antagonists are yet to demonstrate significant benefit in humans, possibly because of a narrow treatment window.[118]

NMDA receptors are upregulated in status epilepticus, and ketamine has been found to significantly reduce seizure burden or completely terminate seizures in refractory status epilepticus.[119,120] Although evidence remains insufficient for routine use, its neuroprotective and antiepileptic properties show promise, particularly in seizures after traumatic or ischaemic brain injury.

Researchers have also considered the neuroprotective properties of ketamine after cardiac arrest. In 2022, Ornowska and colleagues[121] conducted a scoping review and highlighted an absence of literature on ketamine's impact on neurological outcomes after arrest but highlighted preclinical studies supporting its use in reducing markers of neuronal death, such as neurone-specific enolase.

NMDA receptors may be important in chronic neurological conditions, including Alzheimer's disease,[122] Parkinson's disease,[123] and Huntington's disease,[124] with the role of NMDA antagonists such as ketamine or memantine being investigated.

Although studies investigating ketamine in Alzheimer's disease are limited, memantine, a low-affinity NMDA receptor antagonist, has been used successfully in the management of moderate to severe Alzheimer's disease. Animal studies indicate that ketamine may offer additional antidepressant effects in Alzheimer's disease.[122,125,126]

In 2020, Bartlett and colleagues[123] found that ketamine could reduce dyskinesia in Parkinson's disease rats without

affecting levodopa's pro-kinetic effects whilst also independently displaying anti-Parkinsonian properties in subjects not receiving levodopa.

Chronic recreational ketamine use has been linked to reductions in grey matter cortical thickness and impairments in short- and long-term memory.[127–129] These deficits may be reversible, as abstinent users show memory improvements after 12 weeks.[130] The clinical relevance of this is unclear, as chronic users often take far higher doses than those used in medical settings for pain or depression management.

Anti-inflammatory and immune modulation

Since early preclinical studies, it has been known that ketamine can regulate local inflammation and prevents excessive inflammatory responses through attenuation of pro-inflammatory mediators, including tissue necrosis factor alpha (TNF-alpha), interleukin 6 (IL-6), interleukin 8 (IL-8), and interleukin 1 beta (IL-1β).[131–135]

Ketamine also reduces inflammatory cell reactivity to TNF-alpha, prevents cell migration to sites of inflammation, and inhibits pro-inflammatory cytokine-mediated nitric oxide production.[136–139]

Ketamine, etomidate, and thiopental significantly reduced IL-1β in cultured human whole blood exposed to an inflammatory liposaccharide stimulus (83.5%, 82.3%, and 67.6% respectively), whereas propofol significantly increased TNF-alpha (172.3%).[140]

Animal studies simulating septic shock found that ketamine reduced pro-inflammatory mediators TNF-alpha and IL-6 whilst improving haemodynamics, arterial oxygenation, and metabolic acidosis. Ketamine also prevented endotoxin-induced liver injury in a dose-dependent manner.[131,141] Some studies have even shown improved survival with ketamine-exposed rats with sepsis.[142–144]

In the absence of inflammatory stimuli, ketamine demonstrates no effect on immune cells responsible for pro-inflammatory cytokine production.[131] Consequently, ketamine is thought of as an immune regulator, promoting immune homoeostasis and balance depending on the stimuli and conditions, rather than as an anti-inflammatory or immunosuppressant. For example, cocaine induces a systemic surge in anti-inflammatory effects through cortisol production, and ketamine co-administered with cocaine attenuates this anti-inflammatory process rather than enhancing it.[145]

Clinical studies of the anti-inflammatory properties of ketamine are limited; however, in 2012, a meta-analysis was conducted. Dale and colleagues[146] found that perioperative intravenous ketamine for patients undergoing cardiopulmonary bypass surgery, abdominal and thoracic surgeries, and cataract surgeries significantly inhibited IL-6-mediated inflammation in the postoperative period. The effect size was found to be longer acting and at least as significant as methylprednisolone, which is renowned for its anti-inflammatory properties.[146]

More recently, interest has grown around the anti-inflammatory properties of ketamine in the context of depression. The 2023 review by Johnston and colleagues[147] highlights the proposed links between depression and chronic inflammation, preliminary evidence for the use of ketamine in this area, and the need for ongoing research.[147]

Tumour inhibition

Ketamine is a useful adjunct in the management of cancer-related pain. However, its oncological benefits may extend beyond analgesia: NMDA receptors are expressed on different cancer cell lines, including glial and neuroblastoma tumours,[148,149] oral squamous cells carcinomas,[150] pancreatic adenocarcinoma cells,[151] hepatocellular carcinoma cells,[152] prostate cancer cells,[153] and gastric cancer cells.[154]

Glutamate antagonists that block NMDA receptors were shown to inhibit the proliferation of colonic adenocarcinoma cells, astrocytoma cells, breast carcinoma cells, and lung carcinoma cells.[155–157] The magnitude of this effect may vary between different cell types. For example, Saito and colleagues[157] demonstrated that lung carcinoma cell lines have greater sensitivity to ketamine than neuroglioma cells; however, both cell types exhibited dose-dependent reductions in cell proliferation and migration and an increase in apoptosis.

Ketamine also significantly reduced lung metastases of mammary adenocarcinoma in rats and inhibited proliferation whilst increasing necrosis and apoptosis in pancreatic adenocarcinoma cells.[151,158] The NMDA receptor antagonist MK-801 reduced proliferation in hepatocellular carcinoma.[152]

In 2019, Duan and colleagues[159] described ketamine as attenuating the malignant potential of cancer cells and preventing cell migration through NMDA antagonism.

The tumour-suppressing properties of ketamine may also relate to immune modulation. In 2018, Zhou and colleagues[160] found that CD69, a leucocyte and natural killer cell activation marker, was downregulated in human lung adenocarcinoma tissue samples, and ketamine upregulated CD69, resulting in an increase in apoptosis of cancer cells.

The potential for ketamine to become a useful adjunct in the management of a wide range of malignancies, particularly in the perioperative period, has led to growing interest in this field of research. Despite this, the exact effect of ketamine on malignancies remains unclear, and some animal studies have demonstrated that induced ketamine addiction in mice can increase breast tumour invasion and size, without affecting proliferation.[161]

In 2024, Rodriguez Arango and colleagues[162] reviewed the evidence for the peri-operative use of ketamine and cancer recurrence. Despite promising preclinical and laboratory studies, evidence in clinical practice is currently lacking and the authors called for further, standardised research in this area to explore the potential oncological benefits of ketamine.

Ketamine safety, side-effects, and toxicity

Ketamine is considered relatively safe because of its higher therapeutic index compared with other anaesthetic agents, with some studies showing ketamine to have a lethal dose (LD_{50}) of more than 100 times the effective dose (ED_{50}), leading some authors to suggest lethal overdose is 'difficult or even impossible'.[6,163]

Ketamine also has low protein binding (up to 50%[164,165]) compared with propofol (98%[166]) and is highly lipid soluble, crossing the blood–brain barrier and reaching therapeutic levels rapidly without significant dose adjustment, even in relatively low circulating protein states or acidosis.[165]

Data on isolated ketamine overdose are limited as it is uncommon in emergency settings, typically occurring as part of a mixed overdose.[167] Case reports involving accidental overdoses of up to 10 times the intended dose of ketamine during paediatric anaesthesia or sedation have resulted in prolonged but complete emergence from anaesthesia, with few or no other complications.[168,169]

Tolerance to ketamine is described by frequent recreational users but is less well defined in the medical setting.[170]

Ketamine and increased intracranial pressure

One of the main controversies surrounding ketamine remains around its use in patients with acute brain injury, particularly those with or at risk of increased ICP. Early work suggested that ketamine could elevate ICP through sympathetic stimulation and increased cerebral blood flow. In fact, these changes were most likely a result of increased arterial carbon dioxide levels in patients with uncontrolled ventilation.[171]

To date, there has been a lack of evidence supporting the deleterious effects of ketamine in brain injury or increased ICP; more recent studies and reviews have not demonstrated any negative effects or have actually found beneficial effects with regard to ICP and cerebral oxygen consumption ($CMRO_2$).[172–175]

It should be noted that the avoidance of hypotension is crucial in managing traumatic brain injury to prevent secondary brain injury, morbidity, and mortality.[176] After brain injury, cerebral autoregulation is disrupted, and blood flow is dependent on systemic blood pressure and ICP. Therefore, avoiding hypotension and maintaining haemodynamic stability is essential for maintaining cerebral perfusion. Ketamine is often the recommended induction agent in these patients because of its haemodynamic properties.[175,176]

Emergence reactions

Emergence reactions or *emergence phenomena* are psychomotor symptoms experienced by some when waking from ketamine anaesthesia. These range from mild disorientation and euphoria to frank delirium with incidence rates between 5% and 30%.[177]

When using ketamine for general anaesthesia or procedural sedation, clinicians often co-administer low-dose benzodiazepines, haloperidol, or propofol to mitigate the risk of emergence reactions. These reactions are less frequent in children and more common in women, with increasing doses and rapid bolus administration.[31,177]

Despite the risk of emergence reactions, a 2024 meta-analysis by Hung and colleagues[178] found that perioperative ketamine significantly improved patient-subjective quality of recovery, pain severity, and psychological symptoms, such as anxiety and depression, without additional adverse events.

Cardiovascular concerns

Ketamine is associated with increased tachycardia, which could be detrimental to patients with stenotic heart lesions or conditions with reduced tolerance to increased oxygen demand, such as severe coronary artery disease.

In 2015, Mazzeffi and colleagues[179] conducted a review of ketamine use in cardiac surgery and cardiac surgical ICU. They concluded that ketamine helps maintain haemodynamic stability in patients with ventricular impairment and can attenuate systemic inflammation associated with cardiopulmonary bypass.

Ketamine can cause arterial hypertension and therefore may increase the risk of stroke or myocardial infarction in patients with severe cardiovascular or cerebrovascular disease, and often, the recommendation is to avoid ketamine use in these groups.[180]

Co-administration of ketamine with other anaesthetic and sedative agents such as clonidine, propofol, or benzodiazepines may attenuate the deleterious cardiovascular effects in at-risk populations.[181,182]

Urological concerns

In the early 2000s, reports began to emerge of persistent urological symptoms in chronic recreational ketamine users. Symptoms included urinary frequency, urinary urgency, dysuria, haematuria, and even incontinence.[183,184] Histological examination of bladder biopsies show changes in keeping with interstitial or ulcerative cystitis and in severe cases these changes can progress to hydronephrosis and secondary renal impairement.[183]

The exact pathogenesis of ketamine-associated cystitis is not known. Current theories include nitric oxide-induced inflammation, IgE-mediated hypersensitivity, microvascular changes, and direct ketamine toxicity.[185–187]

Ketamine-associated cystitis is unlikely to be a significant risk to patients in the perioperative setting as it appears to be linked to frequent use over extended periods; Rodent models have demonstrated the dose and duration of exposure-dependent relationships.[185,186]

Pathological changes and symptoms appear to decrease in a time-dependent fashion with abstinence from ketamine. Recent reviews by Castellani and colleagues[185] and Anderson and colleagues[186] both emphasise the importance of abstinence in the management of ketamine-associated cystitis, stating that this is usually enough to improve urological symptoms and over time allow the urothelial lining of the bladder to normalise.

Other concerns

Ketamine can cause frequency-, duration-, and dose-related derangements of liver function tests with associated biliary system dilatation and irregularity of the intra- and extrahepatic ducts. Clinical significance is not clear; however, cessation of ketamine typically reverses these abnormalities over several months.[188]

Early studies suggested that ketamine may cause an increase in intraocular pressure.[189] However, subsequent work has demonstrated that ketamine does not produce a clinically meaningful increase in intraocular pressure.[190,191]

Ketamine can cause hypersalivation and bronchorrhoea, although this appears to be rarely of clinical significance.[192,193]

Ketamine is considered a drug of abuse, and its misuse may dissuade clinicians from using it in medical practice. Despite increasing recreational use, there are very few statistics available on ketamine-related deaths.

Corkery and colleagues[194] conducted a thorough review of the deaths associated with recreational ketamine use in England and Wales over the period of 2010–2019. They presented data directly accessed from the Office for National Statistics

(ONS)that show that between 2010 and 2018, a total of 116 deaths related to ketamine were registered in England and Wales.[194] Over the same period, the ONS reported 739 deaths linked to ecstasy or MDMA, 3279 cocaine-associated deaths, and 9922 relating to heroin or morphine.[195]

Summary

In summary, ketamine was discovered in 1962 and is primarily known as an NMDA receptor antagonist that provides dose-dependent analgesic, sedative, and anaesthetic effects. Ketamine exerts effects on NMDA, dopaminergic, serotonergic, adrenergic, cholinergic, opioid, and sigma receptors resulting in diverse and potentially beneficial properties in a variety of clinical settings.

Limited adoption in routine practice over the past 50 years is partly attributable to stigma relating to side-effects and potential for abuse. The evidence presented here suggests that at least some of these concerns, namely regarding ICP, now appear antiquated, with significant evidence refuting early concerns.

This review discusses the diverse therapeutic potentials of ketamine across various fields and emphasises the need for continued research, particularly in areas relevant to anaesthesia and perioperative medicine, such as acute and chronic pain management, ICU sedation, and even tumour suppression, in those undergoing surgical resection of malignancies.

Authors' contributions

Responsible for concept, review of literature, and collecting of source papers, and drafting and refining this review article: NR
Oversight and expert advice, revising and approving the article before submission: SH, MCB, JB

Declarations of interest

SJH is a Trustee and Chair of the Board of the *British Journal of Anaesthesia*. In the past 5 years, he has acted as a panel member for Edwards Lifesciences and is in receipt of research support from Abbott. The remaining authors declare no conflicts of interest.

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