Review

Ketamine, an Old–New Drug: Uses and Abuses

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Abstract: Ketamine as an old - new drug has variety of clinical implications. In the last 30 years, ketamine has become popular for acute use in humans. Ketamine at standard doses is principally utilized for the induction and maintenance in surgical procedures. Beside its use in anesthesia and analgesia, recently studies had shown that ketamine find the place in the treatment of asthma, epilepsy, depression, bipolar affective disorders, alcohol and heroin addiction. Its mechanism of action is complex, but it mostly acts as a noncompetitive antagonist at the N-methyl-D-aspartate (NMDA) receptor. Ketamine is generally considered relatively secure and does not result in serious adverse effects when used at low doses and for short periods- Also, ketamine is known as a powerful psychostimulant. During the past decade, ketamine has been one of the commonly abused drug.

Keywords: ketamine; analgesia; anesthesia; clinical implications; abuse

1. Introduction

Ketamine (2-chlorohenyl-2-methylamino-cyclohexanone) initially known as "CI-581" in chemical structure, is a phencyclidine (PCP) derivative. Calvin Stevens invented the substance called ketamine in 1962. in the Parke-Davis Pharmaceutical Company [1,2]. Its mechanism of action is complex, but it mostly acts as a noncompetitive antagonist at the N-methyl-D-aspartate (NMDA) receptor. Today, ketamine at standard doses is principally utilized for the induction and maintenance in surgical procedures. Due to its quick induction and rapid recovery, its use has been reported in both veterinary and human surgery. In the last 30 years, ketamine has become popular for acute use in humans, especially for parenteral administration of the anesthetic in pediatric patients [3]. Ketamine is used in anesthesia in the emergency department tbut it has shown promising therapeutic potential for the treatment of different disease states, such as depression and asthma. However, due to its properties, dose- and duration-related neurological and peripheral adverse effects are usually reported. Ketamine is known as a powerful psychostimulant, and because of its rewarding and reinforcing effects, it has become a recreational drug, accounting for the steady worldwide increase in its non-medical use [4–6].

2. Ketamine pharmacokinetics

Ketamine can be in two isomeric forms, S (+) ketamine and R (-) ketamine. The S (+) isomer is the active enantiomer, and it has several benefits over the R (-) form. It exhibits a four-fold greater affinity for the NMDA receptor and has twice the analgesic potency and fewer psychomimetic effects than the R (-) isomer. Ketamine is commercially available as a chiral compound consisting of a mixture of both [7]. Ketamine has a pKa of 7.5 and a molecular weight of 238 Da. It is a highly lipid-soluble drug, which accounts for the rapid onset of action as it can easily cross lipid barriers such as

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the blood-brain barrier.The most efficient administration route is intravenously with a bioavailability of 99%, comparing to intramuscular and epidural administration (with bioavailability of 93% and 77%, respectively) [8–10]. Peak plasma concentrations are observedwithin 60 seconds of administration of a single intravenous bolus, with duration of action of 10-15 minutes. As can be seen with other intravenous induction drugs, the effect of single-dose injection is largely terminated due to the rapid redistribution of the drug to other inactive peripheral tissues with high lipid contents (adipose tissue, skeletal muscle, etc.), resulting in a distribution half-life of 7-11 minutes. The intranasal route of application is easy and promotes fast systemic absorption, due to rich vascularization and permeability of the nasal mucosa [11–13]. Oral administered ketamine has a delayed effect of 15–30 min which is the result of first-pass metabolism, which occurs primarily in the liver and involves N-demethylation by the cytochrome P450 enzyme system. Its primary active metabolite is norketamine, which is less potent and is transformed through hydroxylation and conjugation into inactive hydrophilic metabolites that are mainly excreted in urine [14,15].

3. Ketamine pharmacodynamics

Ketamine primarily exerts its analgesic, anesthetic, and psychomimetic effects via antagonism of NMDA receptors in the CNS. In the spinal cord's dorsal horns, the antagonistic effect on NMDA receptors results in interference with pain transmission, leading to profound analgesia and prevention of central sensitization [16,17]. These effects cumulatively lead to amnestic, analgesic, and dose-dependent anesthetic actions, as well as cataleptic and unique-to-ketamine dissociative states. In the dissociative state produced by ketamine, the patient appears to be awake with eyes remaining open but detached from the surroundings [18]. The main contributor to the antidepressant actions is the blockade of NMDA receptors, which causes the activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, leading to a variety of downstream signaling pathway neurotransmissions in the limbic system. The activation of AMPA receptors results in downstream effects that upregulate brain-derived neurotrophic factor (BDNF) and activate signaling receptor tropomyosin receptor kinase B (TrkB).

Moreover, ketamine activates the mammalian target of rapamycin (mTOR) pathway and causes the deactivation of glycogen synthase kinase 3 (GSK-3), as well as inhibition of the phosphorylation of the eukaryotic elongation factor 2 (eEF2) kinase [19–22]. The active metabolite of ketamine, hydroxynorketamine, does not exhibit significant interactions with the NMDA receptor but indirectly activates AMPA receptors and may therefore also contribute to the rapid-onset antidepressant effects of ketamine [23]. By recent studies, ketamine can have antidepressive effects because it can inhibit laternal habenula which is known as "anti-reward center" [24,25]. Ketamine can block muscarinic acetylcholine receptors, voltage-gated calcium channels, and descending monoaminergic pain pathways [26]. The drug exhibits some effects on opioid receptors by acting as a partial agonist that has a greater affinity for the mu and kappa receptors. Ketamine can upscale the effects of gamma-aminobutyric acid (GABA) synaptic inhibition, induce activation of dopamine release, and reduce the presynaptic release of glutamate. Some local anesthetic properties are also observed, possibly through its ability to inhibit neuronal sodium channels. In the periphery, ketamine stimulates the sympathetic nervous system and results in cardiovascular symptoms (increased heart rate, cardiac output, and blood pressure) through blockage of the reuptake of catecholamines. Ketamine also inhibits neuronal uptake and increases serotonergic activity, which is thought to underlie associated nausea and vomiting. In addition, ketamine induces catecholamine release and stimulates β2 adrenergic receptors, leading to bronchodilation [27,28].

4. Clinical indications

Since ketamine was approved by Food and Drug Administration (FDA) in 1970, it is used as an anesthetic for diagnostic and surgical procedures but without muscle relaxation, as an anesthetics for the induction before general anesthetics for its maintenance, and in combination with other anesthetics such as nitrous oxide. Its use as an anesthetic was first recorded on American soldiers during the Vietnam War. In the 50 years since then, ketamine has gained recognition in clinical

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practice; it is used for both veterinary and human clinical anesthesia and is still a popular topic in medical research [29–31]. Ketamine has been applied to treat a variety of diseases. It is effective in disorders such as depression, bipolar affective disorder, chronic pain, asthma, and even in the treatment of alcohol and heroin addiction.

5. Anesthesia

Ketamine was once considered to be ideal for general anesthesia, however, it was quickly revealed to possess a relatively high risk of psychological adverse effects.When recovering from ketamine anesthesia, patients often report unusual symptoms, such as hallucinations, delusions, confusion, and sometimes "out-of-body" and "near-death" experiences, which has led to the discontinuation of ketamine from mainstream anesthetic usage in humans. Still, ketamine and its commercial combinations, due to their unique properties (including profound analgesia, stimulation of the sympathetic nervous system, bronchodilation, and minimal respiratory depression), are an important alternative to other intravenous anesthetics and are therefore in extensive use in specialized clinics, especially in pediatrics, psychiatry, and dentistry [32–34].

One of the prime candidates for ketamine anesthesia is critical care patients with cardiorespiratory disorders. Considering that ketamine, apart from inhibiting the NMDA receptors in postsynaptic neurons in the brain to induce anesthesia, can also increase or maintain cardiac output as well as cerebral blood flow by peripheral inhibition of catecholamine reuptake [35]. It was shown that ketamine in the combination with dexmedetomidine induced good efficacy and sedation, less intraoperative use of anesthetics, less arrhythmias and shorter recovery time in pediatric patients during cardiac catheterizations. Bolus injection which contained ketamine (1 mg/kg) and dexmedetomidine (1 mg/kg) was superior comparing to midazolam-ketamine combination in pediatric patients [36,37]. In adults, the common intravenous dose of ketamine for induction of anesthesia is 0.5-2 mg/kg, and the maintaince the dose is 1-2 mg/min. The doses which are recommended for maintenance vary between 15-90 mcg/kg/min [38]. Ketamine suppresses respiration to a lesser degree than other anesthetic drugs. Also, it induces bronchodilation and analgesic effect what is important in patients who have hypersensitive airway diseases. On the other hand, the use of ketamine might be harmful in patients with limited right ventricular functional reserve and increased pulmonary vascular resistance [39,40].

Recent studies focus more on using ketamine in regional anesthesia and have shown that ketamine is safer and more effective than in general anesthesia. Its use as an anesthetic agent at the surgical site provides adequate analgesia without significant side effects in children undergoing cleft palate surgery. As a rescue analgesic, for a peaceful sleep pattern and early resumption of feeding, ketamine is superior to bupivacaine [41]. Ketamine is also commonly used as an add-on in local and regional pediatric anesthesia [42]. Ketamine can be used for sedation and analgesia during local or regional anesthetic procedures in intravenously administered low doses of 0.5 mg/kg in combination with intravenous diazepam or midazolam or as single drug low dose ketamine of 5-25 mg/kg/min [43,44].

6. Analgesia

Ketamine has been shown to effectively alleviate both acute and chronic pain by inhibiting NMDA receptors in the CNS, thereby preventing the amplification of pain signals. Recent studies have revealed the acute analgesic effect of ketamine in pain management. For instance, a dose of 0.5 mg/kg given intravenously before surgery provided analgesia for up to 24 hours after surgery in patients undergoing appendectomy and cholecystectomy. The same dosage regimen of intravenous 0.5 mg/kg is also safe and effective to use after tonsillectomy for pain control [45–48]. In addition, intravenous low-dose regimens in the 0.25-0.5 mg/kg range as an initial bolus followed by 50-500 μg/kg/h have been proposed for postoperative analgesia and to reduce exogenous opioid-induced hyperalgesia [49]. The use of low doses of ketamine in the emergency department in a bolus of 0.2-0.3 mg/kg over 10 minutes with a subsequent infusion of 0.1-0.3 mg/kg/h as an alternative or add-on to commonly used opioids like morphine, is recommended for pain management [50]. In addition,

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ketamine is currently one of the most significant adjuncts in helping to achieve the desired result when administered at drug-specific regimens and at proven effective dosages throughout the perioperative period. A low dose of ketamine applied intravenously with fentanyl reduced pain scores without increasing the side effects in pediatric patients suffering from pectus excavatum [51,52].

The action of ketamine in opiate tolerance and hyperalgesia, combined with its direct analgesic activity, has encouraged its increasing use in chronic pain states. In a newer study, intrathecal ketamine infusion was shown to immediately relieve the painful myoclonus in the lower extremities associated with opioid-induced hyperalgesia caused by high-dose intrathecal hydromorphone therapy [53]. Another study presented promising results of the use ofketamine for chronic pain management. Through its effects on the NMDA receptor in the CNS, ketamine inhibited central sensitization and was effective in treating severely ill patients with generalized complex regional pain syndrome (CRPS) [54,55]. Ketamine is also a very effective analgesic for other chronic pain syndromes, including chronic pancreatitis pain, postherpetic neuralgia, and it can also be used as an effective adjunct to epidural corticosteroid therapy for chronic pain, such as chronic lumbar radicular pain [56,57]. In small doses, 0.1-0.5 mg/kg ketamine can be used to treat pain associated with movement and neuropathic pain [58]. Ketamine is the most effective for pain relief when used in combination with an opioid, and these types of combinations could be particularly useful in managing cancer pain [59,60].

7. Sedation

Ketamine exerts its sedative effect by enhancing the endogenous antinociceptive system, thereby increasing the descending inhibitory serotonergic pathway [61,62]. Sedative and analgesic effects of ketamine are used in burn patients because of good maintance of respiratory function. [63].Due to the induction of dissociative sedation,the use of a low doseof ketamine in procedural sedation for both adults and children in the emergency department for various painful and emotionally disturbing procedures has gained much support over the last decade. Sedation can be achived by the intravenous or intramuscular injection of ketamine. In children ketamine should be used intranaly ranging from 0.5-9 mg/kg. Low doses of ketamine in combination with low doses of propofol provide effective and safe analgosedation for short surgical procedures in pediatric emergencies, andin adults undergoing colonoscopy and short gynecological procedures [64–66]. In addition, ketamine can be used for patients in a critical care unit as it provides the analgosedation effect and has favorable effects on hemodynamics and ventilation. Ketamine has an anti-inflammatory effects, stimulates cardiovascular system and decreases inotropic effects, which makes it convenient for use in septic patients [67]. It was shown that ketamine in patients with intracranial hypertension undergoing mechanical ventilation effectively decreased intracranial pressure (ICP) and avoided an increase in ICP during distressing interventions without lowering the blood and cerebral perfusion pressures. Therefore, the combination of ketamine with benzodiazepine could be used for traumatic brain injury, such as intracranial hypertension in emergencies [68].

Different sedative medications have been studied for safe and effective use in young, uncooperative patients in pediatric dentistry. Ketamine given alone was reported to have side effects and is mainly used in combination with other drugs such as midazolam to prevent side effects and achieve the desired sedative effects [69]. The mixture of ketamine and midazolam, when administered intranasally,produces moderate sedation in pediatric patients who would otherwise require general anesthesia. This combination therapy has also effectively reduced anxiety scores in young patients referred for treatment under general anesthesia [70].

8. Depression

Depression is the most common chronic and crippling mental illnesspresent in modern-day society associated with high mortality and cost for public health services [71]. It was shown that ketamine rapidly increases the activity of synaptic connections in the cortical and hippocampal neurons and appears to affectconsciousness and neuronal changes associated with stress. This is

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achieved by rapidly inhibiting the NMDA receptor in the CNS by initiating a presynaptic release of glutamate, thereby causing indirect activation of the AMPA receptor in the limbic system. This leads to the activation of mTOR pathways and upregulation of BDNF, which produce changes in synaptic plasticity. This cascade results in enhanced regional activity of the excitation network, including changes in neuroplasticity, which leads to increased synaptogenesis and synaptic potentiation in the limbic system. The advantage of ketamine compared to other traditional antidepressants is its rapid antidepressive action because it bypasses the serotonin pathway and directly leads to increased glutamate levels in the brain [70]. Manystudies that have focused on the effects of ketamine on major depressive disorder suggest a significant and rapid improvement of depressive symptoms after a single ketamine infusion [72,73].Conversely,onestudy assessed the efficacy of repeated intravenous doses of ketamine for depressive patients in which most of the studied patients relapsed [74]. Although preliminary results have shown positive responses, further research should focus on establishing optimal doses for maximal benefits and the best route of administration.

9. Bipolar affective disorder

Bipolar affective disorder, as psychiatric disorders, is characterized by remittent episodes of elevatedmood and depression, with changes in activity levels. About6% of patients die from suicide in the two decades after diagnosis [75]. Treatment is conducted whether mania or depression predominates. One study showed thatadministering ketamine sublingually every 2-3 days or weekly to patients suffering from bipolar depression produceda rapid and robust effect on mood in 77% of cases [76]. In another study, the rapid antidepressant effect of ketamine was observed in several patients with bipolar depression who were given ketamine by intravenous infusion and was maintained for two weeks [77]. In addition to adult patients, children also exhibitedsignificant improvements in mood and behavior after intranasal ketamine administration [78]. This effect is a result of mainly due to ketamine inhibitory action on the NMDA receptor thatleadsto significant increases inglutamate levels in the cortex [79]. These studies have demonstrated the short-term antidepressant and anti-suicidal effects of ketamine in patients with bipolar disorder.

10. Asthma

Asthma is characterized by symptoms of intermittent dyspnea, cough, and wheezing, as a result of bronchial hyperresponsiveness to a variety of stimuli [80]. Typically, therapy is based on inhaled beta-2 agonists, antimuscarinics, and corticosteroids [81]. Ketamine therapy has been researched clinically in the setting of acute asthma attacks. Many studies have shown thatketamine is aneffective drug for the treatment statusasthmaticus. Mechanical ventilation could be avoided if ketamine was used asadjuvant drug in standard treatment protocols [83]. The first example of its use was observedin a 13-year-old child with severe asthma who regained consciousness 30 minutes after continuous intravenous infusion of ketamine [82].It was reported that intravenous ketamine administration improved the symptoms in children with severe asthma. Also, mechanical ventilation had been avoided [84]. Gas exchange was improved in mechanically ventilatedpatients who had remittent bronchospasmafter ketamine infusion [84]. These effects could be explained by several mechanisms, which include inhibition of the NMDA receptor in the airways leading to relaxation of tracheal smooth muscle and bronchodilation, decrease of the nitric oxide levels mediating bronchospasm by inhibition of mRNA overexpression, and protein induction by nitric oxide synthetase. As an antinflammatory agent, ketamine decreases cytokine production, reduces the macrophages, and prevents catecholamine reuptake in the periphery,which increases the free norepinephrine levels and produces a more pronounced effect on the beta-2 receptors, leading to bronchodilatation [85–88]. Ketamine is considered the bronchodilator of choice in rescue therapy for refractory status asthmaticus in the intensive care unit (ICU). A loading dose of 0.1-0.2 mg/kg followed by an infusion of 0.15-2.5 mg/kg/h is used in these situations [89]. While more studies are needed, current findings suggest that ketamine use in status asthmaticus is beneficial.

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11. Epilepsy

Epilepsy typically manifests as sudden, brief episodes of altered or diminished consciousness, involuntary movements, or convulsions [90]. In epileptic seizures glutamate suffusionhas an important part. Antagonists of glutamate receptors, especially ionotropic NMDA and AMPA receptors, have gained much attention in epilepsy therapy. In humans, ketamine has shown to be promising in treating status epilepticus, and its use has also been noted in some neurological intensive care units in cases of prolonged seizures [91]. The combination of drugs such as ketamine and propofol has been given as replacement therapy for seizures as clinical effectiveness of electroconvulsive therapy [92]. Evidence suggests that the NMDA inhibitory effect of ketamine shields neurons from glutaminergic damage during prolonged seizures [93]. A retrospective multicenter cohort study revealed that ketamine is relatively effective and safe for use in treating status epilepticus. In the study, permanent control of the treatment of the refractory status epilepticus was achieved in about two-thirds of patients, whereas ketamine contribution to permanent control was observed in one-third of episodes [94]. Ketamine is a safe, effective, readily available, and cost-effective therapeutic agent for managing refractory status epilepticus in patients with hemodynamic instability.

12. Treatment of alcohol and heroin addiction

Despite years of research into the causes and treatment of addiction, it remains a global problem with an enormous problem with a huge economic burden due to its impact on productivity, healthcare costs, and crime [95,96]. Approximately 5% of the world's adult population suffers from an alcohol use disorder. In the United States, the number of people dying from opioid overdose deaths has increased by 120% between 2010 and 2018 [97,98]. The possible mechanisms of ketamine in treating addiction include increasing neuroplasticity and neurogenesis, obstructing substantial neural structures, curing symptoms of depression, stopping the reconsolidation of memory, inducing mystical experiences, and enhancing efficiency of the therapy [99]. Ketamine-assisted psychotherapy (KPT) sessions have been used to treat heroin and alcohol addiction with good results. KPT in high doses (with ketamine at a dose of 2.0 mg/kg) in comparison with low doses (with ketamine at 0.2 mg/kg) in heroin addicts enticed a full psychedelic experience. Also, high dose KPT induces higher rate of abstinence, reduction in heroin craving, and a greateralterationsin "nonverbal unconscious" emotional standpoints [100]. In another randomized study with heroine-dependent patients, 50% of the KPT group remained abstinent when compared with just 22.2% in the control group. Likewise, attenuation of opiate withdrawal symptoms was demonstrated with ketamine, pointing toits potential use in treating drug addiction [101]. Ketamine has been shown to have beneficial effects in proceeding abstinence from alcohol and heroin.

13. Adverse effects and interactions of ketamine

Ketamine is generally considered relatively secure and does not result in serious adverse effects when used at low doses and for short periods. However, side effects can occur in up to 40% of patients with continuous subcutaneous infusion of ketamine. These include dizziness, blurred vision, altered hearing, hypertension, nausea and vomiting, vivid dreams, and hallucinations [102]. Due to its NMDA receptor-blocking action, ketamine may trigger an excessive release of glutamate and thus cause cortical excitability, which can lead to psychotic behavior and cognitive abnormalities [103]. The acute effects of ketamine administration can cause dose-dependent positive and negative schizophrenia-like symptoms and are mostly related to abnormal activation of the prefrontal cortex and limbic structure. In both fetal and neonatal development, a 5-h exposure may be sufficient to induce a significant neuroapoptotic response due to the sensitivity of the brain to the apoptogenic effects of ketamine. The neuroapoptotic process induced by ketamine-related NMDA receptor blockade involves bcl-2-like protein 4 (Bax) translocation to mitochondrial membranes and cytochrome c efflux to the mitochondrial outer surface, followed by caspase-3 activation [104].

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Repeated doses of ketamine can result in serious toxicity and can induce chronic health problems. Because the main path of ketamine elimination isthrough urine, it can cause damage to the upper and lower urinary tracts, leading to symptoms such as increased urinary frequency, urgency, dysuria, hematuria, and cystitis. Ketamine-induced ulcerative cystitis is a condition that can have a severe and potentially long-lasting effects on ketamine users. These side effects are seen in clinical practice in individuals who abuse ketamine, and with dose reduction, their incidence canbe reduced [105–109]. Animal research hasproved that chronic ketamine use can exacerbate neuromuscular strength and nociception. In addition, the mesolimbic, mesocortical, and entorhinostriatal systems are vulnerable to chronic ketamine administration. Dysfunction of these neural systems has been connected to several neuropsychiatric disturbances (depression, ADHD, etc.). The neuroapoptotic effects of long-term ketamine use are similar to aging processes and Alzheimer's disease [110–112]. Regarding psychiatric side effects, depression was found to worsen over a year in both daily and former ketamine users. Evidence suggests that long-term CNS depression is likely the result of an interaction between ketamine and gabapentin [113,114]. Ketamine as an NMDA receptor blocker reduces neuroplasticity after long-term use. Studies have shown that repeated use of ketamine over a long period of time significantly impairs both short-term and long-term memory, visual recognition, and spatial working memory. However, memory impairment appears to be reversible [115–117]. There is little evidence of a link between chronic, heavy ketamine use and a diagnosis of a psychotic disorder such as schizophrenia. Therefore, the effect of ketamine on psychosis is questionable and needs further research [118–120].

Although ketamine relaxes bronchial smooth muscle, the drug may result in airway obstruction in 10-20% of users, especially in children where the risk of laryngospasm due to increased salivation must be considered [121,122]. Long-term use of ketamine can cause significant ventricular myocardial apoptosis, fibrosis, and sympathetic denervation, leading to arrhythmias. An increase in liver enzymes has been observed with repeated use of ketamine in chronic pain [123,124]. Finally, other problems caused by chronic administration of ketamine include severe abdominal pain, dilatation of the bile ducts and bilateral corneal edema [125,126].

Ketamine interaction with certain drugs should be noted. Specific agents are described in Table 1. The simultaneous use of ketamine and drugs that reduce liver metabolism by inhibiting CYP3A4 enzymes of the cytochrome P450 enzyme system (i.e., clarithromycin, ketoconazole) can increase the serum levels of ketamine with serious consequences. The administration of ketamine with other CNS depressants such as tramadol, alcohol, and opioids increases the risk of respiratory depression, profound sedation, and coma. Increased neuromuscular blockade is reported after concomitant administration of tubocurarine and atracurium. Lastly, an increased risk of seizure development is seen in patients administered theophylline. The useof ketamine for general anesthesia or chronic pain in young children and pregnant women should be carefully considered as prolonged exposure can negatively affect fetal or young children's brain development [127].

Table 1. Ketamine interaction with certain drugs.

Drugs/Drug Groups	Side Effects/Interactions
Alcohol	Central nervous system depression (respiratory depression, sedation, coma)
Amphetamine/Dextroamphetamine/Lisdexamfetamine	Cardiac effects (arrythmia)
Benzodiazepines (clonazepam, lorazepam)	Central nervous system depression (respiratory depression, sedation, coma)
CYP3A4 inhibitors (ketoconazole, clarithromycin, grapefruit juice)	Increase plasma drug concentrations of ketamine
Doxazosin	Hypotension
Doxepin	Central nervous system depression (respiratory depression, sedation, coma)
Hydroxyzine	Central nervous system depression (respiratory depression, sedation, coma)

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Haloperidol	Additive central nervous system effects(dizziness, drowsiness,impairment in thinking)
Mirtazapine	Additive central nervous system effects(dizziness, impairment in thinking, judgment)
Nortriptyline	Central nervous system depression (respiratory depression, sedation, coma)
Neuromuscular blockers (tubocurarine, atracurium)	Neuromuscular blockade
Propranolol	Hypotension
Pregabalin	Central nervous system depression (respiratory depression, sedation, coma)
Trazodone	Central nervous system depression (respiratory depression, sedation, coma)
Theophylline	Increased risk of seizures

14. Ketamine abuse

The first reports of ketamine abuse were described in the late 1960s. In the 1970s and 1980s, widespread abuse was reported in North America, followed by Europe and Asia. In the mid-1990s, the use of ketamine as a recreational drug became common in "rave" and nightclubs in Europe and the United States. During the past decade, ketamine has been a commonly abused drug in Hong Kong and China [128–130]. Although ketamine is a controlled substance, its abuse has enlarged in the recent years [131]. Ketamine is most commonly used in powder form for inhaling through the nose, but it is also available in liquid and tablet form. Ketamine is mainly known under the names of ''special vitamins K'', ''super-K'', and ''K''. The most attractive aspects of ketamine use are "the feeling of melting into the environment", "visual hallucinations" and "out-of-body experiences" and "laughs" [132]. At high doses, ketamine induces a more severe state of dissociation, often referred to as a "K-hole", where the user experiences intense dissociation to the point where perceptions seem completely detached from their previous reality [133]. This state of dissociation is unique to the drug and is one of the main reasons for its abuse. Although the full mechanism of ketamine's dissociative effects is not yet fully understood, there is a link between cognitive impairment and schizophrenia-like symptoms associated with inhibition of the N-methyl-D-aspartate receptor [134]. Concerning the patterns of non-medical ketamine use, a survey in 2009. reported 1285 individuals who had used ketamine in the previous year. When they were asked about doses used in a typical session, one third reported using less than 0.125 g, another third reported using 0.25-0.5 g, and a final third of respondents reported using more than 1 g in a single session, with 5% using regularly more than 3 g per session. The mean number of consecutive days of ketamine use was 3.5 days, with 11% reporting at least 7 consecutive days [135]. Ketamine is often used with other medications. Another report from an emergency department in Hong Kong showed that patients with acute ketamine toxicity simultaneously used substances such as alcohol, cocaine, and MDMA [136]. Changes in the brain can cause different color perception, disturbances in memory, attention, cognition.The two most common side effects of ketamine abuse are gastrointestinal and kidney problems. One retrospective study showed that ketamine abusers usually have upper gastrointestinal symptoms, such as an abdominal pain. The cause of the pain may be biliary abnormalities, which can be explained by smooth muscle relaxation achieved by ketamine's NMDA receptor blockade. Another common gastrointestinal complication is liver injury [137,138]. Severe lower urinary tract symptoms (LUTS), including increased urination, urinary urgency, and dysuria, which can lead to interstitial cystitis, have been commonly reported in active ketamine users. Connection between long term ketamine use and the incidence of cystitis is found, but the wright mechanism is unknown. Also, it was reported link between ketamine abuse and irreversible kidney damage, such as hydronephrosis and renal [139–141]. Deaths are rarely associated with ketamine alone, due to its wide therapeutic range [142]. In general, people with acute ketamine toxicity do not need medical attention. Rest in a quiet area with

minimal auditory and visual stimulation and sedation is often all that is needed, especially for people with hallucinations and other neuropsychological effects. Some agitated and aggressive patients require benzodiazepine therapy such as diazepam or lorazepam. If tachycardia, hallucinations, and hypertension do not improve within 2–3 hours with the above treatment, they should be treated accordingly [143,144]. There is no specific treatment for patients who abuse ketamine. Based on the main pharmacological effect of ketamine, attempts have been made to treat ketamine addiction by modulating the glutamatergic system. A recent study reported that the frequency and daily dose of ketamine use were significantly reduced in chronic ketamine users who received lamotrigine, a glutamate release inhibitor [145]. Although ketamine is a relatively safe medical substance, its abuse has serious consequences for individuals and society.

15. Conclusion

Ketamine is a non-competitive NMDA receptor blocker that is often used in human and veterinary medicine under strictly controlled conditions, as an analgesic and sedative agent. This is a good example of how an existing drug with a relatively stable and established use in clinical practice can be repurposed for multiple uses. The choice of treatment depends on the pathological condition and is effective for diseases such as depression, bipolar disorder, epilepsy, asthma and heroin and alcohol addiction. However, due to its unique dissociative effects, ketamine is often used illegally as a recreational drug, mainly by young adults. The side effects caused by repeated use of ketamine and the mechanisms behind them should be further investigated to find solutions to combat them.

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