

Intravenous ketamine in the treatment of substance use disorder

Abstract

Background: Substance use disorders (SUD) represent a critical public health issue, significantly contributing to global morbidity and mortality. Traditional pharmacotherapies for SUD have limited efficacy, necessitating innovative treatment approaches. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has shown promise beyond its anesthetic and analgesic uses, demonstrating potential therapeutic effects in SUD management.

Objective: This study explores the efficacy of intravenous ketamine as a therapeutic intervention for SUD, including alcohol, opioids, cocaine, and other substances.

Methods: A comprehensive review of clinical trials conducted in preclinical studies essential to assessing the potential effects of intravenous ketamine on various SUDs. The review focused on ketamine's impact on withdrawal symptoms, cravings, abstinence rates, and overall treatment outcomes across different substances.

Results: Studies indicate that ketamine infusions, combined with psychological therapies, significantly increase abstinence days and reduce alcohol intake. Ketamine also appears effective as an adjunctive treatment for benzodiazepine-resistant alcohol withdrawal. Clinical trials reveal that ketamine can alleviate withdrawal symptoms and reduce cravings. High-dose ketamine administration showed a sustained reduction in craving and increased abstinence rates compared to lower doses. Ketamine treatment significantly reduces cocaine-seeking behavior and cravings in both preclinical and clinical settings. Participants reported reduced cocaine consumption and cravings post-infusion, with effects lasting up to several weeks. Preliminary studies also suggest ketamine's potential in reducing nicotine self-administration and aiding cannabis use disorder treatment when combined with behavioral therapies.

Conclusion: Intravenous ketamine shows promise as a treatment for various substance use disorders by reducing cravings and withdrawal symptoms and promoting abstinence. However, further research with larger sample sizes and extended follow-up periods must confirm these findings and establish ketamine's long-term efficacy and safety in SUD treatment.

Keywords: ketamine, substance use disorder, alcohol use disorder, opioid use disorder, cocaine use disorder, intravenous therapy, NMDA receptor antagonist.

Substance use disorders (SUDs) are a significant health issue in the United States and around the world, contributing to illness and death. The mortality rate due to substance use disorders has reached epidemic levels, with the United States alone accounting for 25% of global overdose mortality. From 2013 to 2016, there was an 88% annual increase in opioid overdose deaths in the United States. The 2020 National Survey on Drug Use and Health (NSDUH) showed that 40.3 million Americans reported a substance use disorder in the past year [1]. Despite advancements in treatments, SUD remains challenging to address.

SUD is characterized by cognitive, behavioral, and physiological symptoms resulting from the harmful use of substances such as alcohol, cannabis, opioids, stimulants, tobacco (nicotine), and others. Critical indicators of SUD include impaired control, cravings, drug seeking, social impairment, risky use, and withdrawal symptoms that are lethal [2].

Withdrawal from alcohol can lead to severe symptoms such as seizures, autonomic dysregulation, hallucinations, agitation, and anxiety. Physiological responses to opiate withdrawal may include nausea, vomiting, diarrhea, muscle pain, excessive tearing, runny nose, fever, dysphoria, and insomnia, often necessitating immediate treatment. Studies have shown that withdrawal symptoms can contribute to relapse in patients with a history of substance use disorder. The majority of accidental deaths in the United States are due to drug overdose, and relapse rates for current substance use disorder therapy range from 40–80% [3].

Despite the increasing prevalence of SUDs, treatment options are limited. Traditional approaches, such as Naltrexone, Acamprosate, Methadone, and Buprenorphine, often face limitations in efficacy, accessibility, and engagement. There is an urgent need for innovative therapeutic interventions and novel pharmacotherapies to address the intricate interaction of biological, psychological, and social factors at the core of this phenomenon. SUDs improve treatment outcomes and promote long-term recovery [4].

Ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist with established safety and efficacy as an analgesic and anesthetic. Still, its unique pharmacological profile sparked interest in its off-label uses, leading to ongoing research into its therapeutic potential beyond anesthesia and analgesia [5]. Ketamine is a prescription drug that, at subanesthetic doses, induces profound psychedelic experiences and hallucinations. These subanesthetic effects are hypothesized as the therapeutic mechanism in the use of ketamine for the treatment of SUD.

The two optical enantiomers of ketamine, S and R, are phenyl cyclohexyl amine derivatives. It was developed in 1964 as a replacement for phencyclidine. In 1970, it was made commercially available as a fast-acting intravenous anesthetic for human use. It is made from phencyclidine

(PCP) to reduce misuse and significant psychotomimetic adverse effects. Ketamine is a desirable drug due to its short half-life and lack of clinically significant respiratory depression. In addition to its anesthetic and analgesic effects, it has antidepressant and anti-inflammatory effects [6].

Ketamine's Mechanism of Action and Its Role in SUD

Ketamine is an anesthetic with dissociative and hallucinogenic effects. It was developed from phencyclidine. It acts as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, for which glutamate is the complete agonist. At subanesthetic doses, ketamine has analgesic and antihyperalgesic effects by antagonizing the NMDA receptor [7]. Ketamine interacts with binding sites (opioid, monoaminergic, cholinergic, nicotinic, and muscarinic) via glutamate-dependent (NMDA receptors) and glutamate mechanisms. Although ketamine binds to GABA and opioid receptors, it is not responsible for its analgesic effects [8]. Additionally, ketamine causes a hyperadrenergic state by stimulating noradrenergic neurons and inhibiting catecholamine absorption, leading to norepinephrine, dopamine, and serotonin release [8]. Ketamine has a chiral structure consisting of two optical isomers. It is oxidatively metabolized by cytochrome P450 (CYP) 3A and CYP2B6 enzymes, resulting in norketamine [9].

Norketamine contains about 20 percent of the analgesic properties of ketamine. However, its pharmacokinetics are obscure [8]. Ketamine is often administered intravenously, although it can be given intranasally, orally, and intramuscularly. Due to substantial first-pass metabolism, oral bioavailability is low, and ketamine is susceptible to pharmacokinetic drug interactions [9].

Rationale for Ketamine in SUD Treatment

Ketamine is a mixture of R and S enantiomers that bind to opioid receptors (μ , δ , and κ). These receptors are the target sites for traditional medications used in treating substance use disorders. Studies have revealed a strong correlation between the onset and course of addiction in people with different substance use disorders and the dysregulation of the glutamatergic system in particular brain regions, such as the prefrontal cortex and mesolimbic areas, -which include the amygdala and nucleus accumbens [4].

Ketamine has been found to improve glutamate homeostasis in the prefrontal cortex, leading to synaptic improvements by increasing spine density in synaptic proteins. According to existing models, ketamine's inhibition of NMDA receptors promotes synaptogenesis by boosting protein synthesis. This causes rapid activation of the mammalian target of rapamycin (mTOR), signaling elevated levels of synaptic proteins in the rat prefrontal cortex [10]. In humans, a decrease in Brain-Derived Neurotrophic Factor (BDNF) serum levels supports the decline in neurogenesis in addiction [11]. Several trials have disclosed that ketamine increases BDNF and treats depressive effects [12]. With reduced BDNF levels in patients with various addictions, this seems to be a

feasible mechanism for ketamine's anti-addictive action. This structural change has been associated with enhanced learning behaviors and may be beneficial in treating substance use disorders. Studies and clinical trials have also shown that intravenous ketamine use reduces significant cravings in people with alcohol, cocaine, and heroin addiction and increases abstinence from the use of these substances [4].

Clinical Studies of Ketamine in SUD Treatment

Alcohol Use Disorder

Several studies conducted on animal models on the therapeutic effects of ketamine in alcohol use disorder suggested that ketamine may be beneficial in treating alcohol withdrawal symptoms and increasing days of abstinence. A study carried out on adult alcohol-preferring rats, when injected with subanesthetic doses of ketamine over three weeks, showed a significant reduction in alcohol intake [13]. Grabski et al. also demonstrated in their study of 96 patients managed for severe alcohol use disorder, placed on three weekly ketamine infusions and psychological therapy, that therapy was related to more days of alcohol abstinence at the 6-month follow-up period, implying a potentially favorable benefit of integrating psychological therapy alongside ketamine medication [14]. Various other studies have also shown that ketamine has also been implicated in helping reduce the dose of benzodiazepine required for the management of alcohol withdrawal syndrome [15,16]. In cases of severe alcohol withdrawal, ketamine has been used as an adjunct for benzodiazepine-resistant alcohol withdrawal symptoms [17].

Opioid Use Disorder (OUD)

"N-methyl-D-aspartate antagonists are effective in alleviating the symptoms of opiate withdrawal. Ketamine, an intravenous anesthetic, is the most potent N-methyl-D-aspartate antagonist currently used in clinical practice.

An investigation was carried out using a randomized, placebo-controlled, double-blind design to assess the impact of ketamine infusion administered subanesthetically on rapid withdrawal from opiates. This clinical experiment included 58 patients who were dependent on opioids. Under general anesthesia, patients were quickly put into an opiate antagonist induction state. Patients received either a subanesthetic ketamine infusion at a rate of 0.5 mg/dl/h or a placebo, which is normal saline, prior to the induction. Subsequent assessments were conducted on the gastrointestinal, respiratory, cardiovascular, and renal responses to opiate antagonist induction, all tracked while the patient was under anesthesia. There were fifty patients in the final analysis. Based on objective opiate withdrawal scales, the ketamine group demonstrated improved control over the anesthetic symptoms, which persisted after the ketamine infusion. There were notable variations between the ketamine and control groups in the anesthetic and early postanesthetic phases. Placebo (normal saline) or a subanesthetic ketamine infusion of 0.5 mg/dl/h. Further evaluations were divided into cardiovascular, respiratory, renal, and gastrointestinal responses to opiate antagonist induction and monitored during anesthesia. The final analysis included 50

patients. The ketamine group showed better control of the anesthesia symptoms based on objective opiate withdrawal scales, which lasted beyond the ketamine infusion itself. Significant changes in the ketamine and control groups were observed in the anesthetic and early postanesthetic phases. As a result of these findings, it was concluded that subanesthetic ketamine infusion was an effective adjuvant in the treatment of precipitated opiate withdrawal [18].

In another clinical study, it was discovered that a higher dose of ketamine significantly reduced heroin cravings in two groups of heroin-dependent individuals who received doses of 2mg/kg and 0.2mg/kg, respectively. Over 24 months, cravings continued to decrease in the high-dose group, while they did not persist for more than a month in the low-dose group. Furthermore, the high-dose group exhibited a higher rate of abstinence during both periods [19]. In a subsequent long-term study, participants among 53 heroin-dependent patients who underwent single or three sessions of ketamine-assisted psychotherapy (KAP) displayed a significantly higher abstinence rate of 50% compared to 22% for those who received only one session [20]. Additionally, it was observed that ketamine might aid in the withdrawal from additional medication required to manage acute opiate withdrawal. However, this was unrelated to treatment outcome at the 4-month follow-up [18].

A 2019 preclinical study, which was carried out on both cocaine-exposed and cocaine-naive rhesus monkeys, showed that there was a reduction in the cocaine-seeking behavior of the monkeys and the effects of cocaine, respectively, 48 hours post-ketamine treatment [21].

A couple of clinical trials have also shown some effectiveness in the use of ketamine for cocaine use disorders. For example, a cross-over trial study was conducted by Dakwar et al. involving 8 participants who had current cocaine dependence with no desire to quit. The study aimed to evaluate the pre-ketamine infusion (at sub-anesthetic doses) and post-infusion results regarding motivation to quit and cravings induced on cue. The volunteers were given three infusions, each lasting for 52 minutes - 0.41mg/kg ketamine, 0.71mg/kg ketamine (which was given after 48 hours), and this was compared to lorazepam 2mg (control). The study found a 60% increase in the motivation to quit from baseline and a reduction in cravings compared to the control at 24 hours post-infusion ($p < 0.012$). A reassessment of the volunteers was done four weeks post-infusion, which showed that the rate of cocaine consumption had reduced significantly in their day-to-day lives [22]

Using the previous model, a study of 20 volunteers with cocaine dependence (not seeking treatments) was conducted by the same group of researchers. This time, they received a single infusion of either 0.025mg/kg midazolam (control) or 0.71mg/kg ketamine over 52 minutes. The effect of ketamine on self-administration, cravings, and reactivity to cocaine cues were considered. At 48 hours post-infusion, there was a substantial reduction in choosing to use cocaine, cravings, and reactivity to cocaine cues ($p < 0.0001$, $p < 0.01$, $p < 0.05$, respectively).

Moreover, the participants still had a general decrease in cocaine use at two weeks post-ketamine administration [23].

Other Substance Use Disorders

Smoking cessation: It is pertinent to develop more therapeutic strategies despite the availability of various pharmacological agents in reducing the addiction to nicotine. Studies were conducted to evaluate the acute administration of sub-anesthetic doses of ketamine in a study involving Both male and female Sprague-Dawley rats who were trained to self-administer nicotine and were injected with... "5, 7.5, and 10 mg/kg of saline. The effects of the number of intravenous infusions during a 45-minute session were measured. The results showed that ketamine treatment significantly reduced nicotine self-administration in a dose-dependent manner. This study highlights the role of glutamatergic ionotropic receptors in addictive behaviors, including drug addiction, such as alcohol and nicotine. Since ketamine is an NMDA antagonist, its effects were impactful in this context. to reduce nicotine self-administration, showing that it could cause a reduction in nicotine addiction [13].

Cannabis use: A clinical trial was done to test the feasibility, tolerability, and potential effects of integrating ketamine with a behavioral platform of motivational enhancement therapy and mindfulness-based relapse prevention in treating cannabis use disorder. Eight cannabis-dependent individuals received motivational enhancement therapy and mindfulness-based relapse prevention behavioral treatments completed in 6 weeks. Participants received either 0.71mg/kg or 0.41mg/kg infusions of ketamine. The outcome of the clinical trial was that the ketamine infusion was tolerated well by the subjects without adverse effects and reduced cravings in subjects. It caused abstinence from cannabis use disorder throughout the six-week duration of the study when combined with behavioral therapy [24].

Safety, Tolerability, and Potential Adverse Effects

Safety profile

Ketamine is water- and lipid-soluble, allowing for flexibility in different administration routes. The optimal route of administration is intravenous, except in emergencies, obese patients, and children. The intramuscular (IM) route has been in use for a long time- it is safe and predictable. Compared to the intravenous route(IV), it is associated with a longer recovery time and a higher rate of vomiting. The oral bioavailability of ketamine is low, but with small doses per os (PO), S- Ketamine can be used as an alternative for repeated intravenous injections. Rapid systemic absorption is associated with repeated intravenous injections. Ketamine should be titrated to the required clinical effect, no matter the route of administration [25]. Studies have shown that ketamine used at a subanaesthetic level is safe; 1.2 mg/kg given intramuscularly was used. The

intravenous route is considered the best route to control blood ketamine levels and is an established conventional route of administration for therapeutic purposes [14].

Adverse Effects

Ketamine increases can be associated with nausea and vomiting. It has a minimal effect on the central respiratory system if given slowly. However, rapid injection can cause apnea. Ketamine also increases the secretion of the salivary gland, leading to increased salivation. So, it is advised to co-administer with atropine (0.01 mg/kg). When used in subanesthetic doses, especially in the treatment of substance use disorders, ketamine causes imaginative dissociative states and psychotic symptoms mimicking schizophrenia. This results from its antagonistic effect on NMDA and semantic and episodic memory impairment. It can cause a floating sensation, vivid dreams, nightmares, hallucinations, and delirium [25].

Dissociative effects of ketamine.

The most commonly reported psychoactive effect after a single subanesthetic dose of ketamine is dissociation. This includes distortions in visual, auditory, or somatosensory stimuli and alterations in the perception of self and time. Positive psychomimetic effects include conceptual disorganization, hallucinations, suspiciousness, and unusual thought content. Adverse psychomimetic effects include blunt affect, emotional withdrawal, and motor retardation. A randomized, double-blinded, placebo-controlled trial conducted by Krystal et al. aimed to ascertain these effects. The study showed that a 40-minute intravenous injection of ketamine at a subanesthetic dose of 0.5 mg/kg led to perceptual aberrations consistent with dissociative states, as well as positive and negative psychomimetic effects within 10 minutes [26]. Ketamine is known to worsen psychotic symptoms in patients with schizophrenia. "Illusions and changes in hearing, vision, and body awareness." have been observed with ketamine use, while the use of R-ketamine mainly causes feelings of relaxation [6].

Memory and Cognitive Impairment: In addition to the dissociative and psychomimetic effects, several studies have identified the impact of the subanesthetic administration of ketamine on cognition. According to studies done by Mathew et al. (2010), ketamine decreases sharpness, concentration, recall, and explicit (episodic and semantic) and implicit (procedural) forms of memory either during or after the dose administration [27]. Moreover, during and right after a 40-minute intravenous infusion of 0.5 mg/kg, there is a decrease in attentiveness, verbal fluency, and delayed recall. However, global cognitive function and immediate recall appear intact during ketamine infusion [6].

Abuse and Risk of Dependency: Ketamine's dissociative effects have made it desirable for recreational use. However, some users may experience agitation or anxiety panic attacks within 10 minutes following an intravenous injection of 0.5 mg/kg; healthy subjects reported feeling "high." A lower 0.1mg/kg dose induced a mild euphoria [28]. Doses of ketamine used for recreational purposes may range from 1 and 2 mg/kg, 50 and 150 mg (intramuscular), 100 and

500 mg (oral), or 30 and 400 mg (intranasal insufflation). These are the various methods by which ketamine abuse can be achieved. At lower doses, users experienced mild stimulatory, dissociative, and hallucinogenic effects, while at higher doses, psychotomimetic symptoms and separation from reality were observed [6].

The most common route of recreational administration is nasal insufflation (inhalation), with intoxication setting in between 5 to 10 minutes and lasting between 45 to 75 minutes. At peak levels of intake, ketamine induces a highly dissociative experience that includes an altered state of consciousness and sensory detachment (referred to as K-hole), which has been equivalent to a near-death experience. At plasma concentrations ranging from 50 to 200 ng/ml (0.21-0.84 uM), ketamine enhances sensory perception (high-intensity of sound), emotional connectedness, and feelings of unreality and out-of-body experience. Dizziness, blurred vision, slurred speech, vomiting, palpitations, and chest pain have also been reported in users. "Using ketamine for an extended period can cause flashbacks.", attentional and other cognitive dysfunctions, and decreased sociability [6].

Emerging and Future Directions

Ketamine, in sublingual and intramuscular forms, has been used for decades by experienced psychotherapists in administering ketamine-assisted Therapy (KAT) [29]. Early addiction treatment trials employed high dosages of 2-3.0 mg/kg via intramuscular injection [20,29], but more recent research generally uses 0.4 mg/kg-0.71 mg/kg supplied intravenously, infused over 40-60 minutes [22].

Emerging ketamine therapy in treating substance use disorders focuses on the application of the ketamine-assisted psychotherapy (KAP) model. It describes specific applications based on dosage and administration method, suggesting lower-dose sublingual administration for sessions involving more active therapist-patient communication and higher-dose intramuscular administration for sessions with closer adherence. to current psychedelic psychotherapy models, such as an inward focus, eye coverings, and music [29]. In 2020, in a randomized controlled trial that paired single ketamine intravenous infusion (0.71 mg/kg) using motivational enhancement therapy for alcohol dependence, it was discovered that ketamine had a significant impact, increasing abstinence rates and reducing the likelihood of alcohol use and heavy drinking. as well as a longer time to relapse over 21 days after infusion, compared with midazolam.[28]. Similar results were replicated in opiate and cocaine use disorders when the KAP model was applied, where it showed abstinence, decreased craving, and lowered the time needed to relapse [22,23]. Although limited combination trials are using intranasal and sublingual ketamine formulations to treat drug use disorders, further research is necessary to explore the possibilities thoroughly.

Substance use disorder has been implicated in the impairment of neurogenesis in adults, with the reduction of serum levels of BDNF neurotrophic factors responsible for neurogenesis. The

mechanism of action of ketamine's antidepressant qualities has already been linked to improving BDNF levels [12]. Hence, BDNF can also be a potentially useful biomarker in assessing the effectiveness of ketamine treatment for SUDs.

Limitations of Current Research and Gaps in Literature

Despite this noteworthy literature, a couple of limitations exist. First, the sample sizes are quantitatively small, and many research studies had under 100 participants. Also, the duration of follow-up of the study participants was relatively short for a chronic disorder, so the extent of the benefits or side effects of ketamine could not be entirely determined. The mechanism of action of ketamine in this disorder is still not distinct, and this might increase skepticism about its use, especially given the fact that it can also be addictive. The generalizability of the study must also be done with caution, if at all, as underrepresented groups form only a tiny percentage of the clinical trials' participants, even though the prevalence of substance abuse is relatively high among them. Furthermore, it is essential to note that there were more studies on the use of ketamine for alcohol use disorder than any other substance.

Conclusion

Substance use disorder is a public health concern globally, cutting across different age groups. Even though there is a lack of preclinical studies on the use of ketamine for this disorder, clinical trials have demonstrated that ketamine improves abstinence while reducing cravings, frequency of use, cue-induced reactivity, and substance self-administration. The psychedelic properties of ketamine have been implicated in these results. However, the various studies considered had small sample sizes. Therefore, a comparatively more significant sample size is necessary to give more credibility to the use of intravenous ketamine in these conditions. Hence, there remains much exploration into the usage of ketamine in different kinds of substance use disorders that require further research.

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