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Intravenous Ketamine in the Treatment of Substance Use Disorder

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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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.

1. INTRODUCTION

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. Hence, there is a need for innovative therapeutic interventions and novel pharmacotherapies to address the intricate interaction of biological, psychological, and social factors [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 phenylcyclohexylamine 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].

2. 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 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].

3. RATIONALE FOR KETAMINE IN SUD TREATMENT

Ketamine is a mixture of R and S enantiomers that bind to opioid receptors (mu, delta, and kappa). 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 revealed that ketamine exerts some of its antidepressant effects by increasing BDNF [12]. Also, because there’s reduced BDNF levels in patients with various addictions, Ketamine’s potential to raise the BDNF level seems to be the mechanism for its 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].

4. CLINICAL STUDIES OF KETAMINE IN SUD TREATMENT

4.1 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 increase days of abstinence. A study carried out on adult alcohol-preferring rats showed a significant reduction in alcohol intake when the rats were injected with subanesthetic doses of ketamine over three weeks [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 administration [14]. Various other studies have also shown that ketamine is implicated in helping to reduce the dose of benzodiazepine required for the management of alcohol withdrawal syndrome [15,16]. And in cases of severe alcohol withdrawal, ketamine has been used as an adjunct for benzodiazepine-resistant alcohol withdrawal symptoms [17].

4.2 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. In a double-blind, randomized, placebo-controlled trial conducted on 58 patients with opiate dependence, patients were placed under general anesthesia and they received rapid opiate antagonist induction. Then, they were administered either a placebo (normal saline) or a subanesthetic ketamine infusion at a rate of 0.5 mg/kg/h prior to opiate antagonist induction. Further evaluations were comprised of three phases: anesthesia, early postanesthetic (48 hours), and remote at 4 months following the procedure. During the anesthetic phase, the reactions to opiate antagonist induction were observed in the cardiovascular, respiratory, renal, and gastrointestinal systems. Changes in serum cortisol concentrations were used as indices for stress response. Early postanesthetic phase assessment was done using the Subjective and Objective Opioid Withdrawal Scales. The Addiction Severity Index questionnaire was used to evaluate the remote effects. In total, 50 patients were included in the final analysis. The Ketamine group showed greater control of withdrawal symptoms, which persisted beyond the ketamine infusion itself. Significant differences between the Ketamine and Control groups were observed in the anesthetic and early post-anesthetic phases. However, there were no discernible differences in outcomes after 4 months. This study concluded that although subanesthetic ketamine infusion had no long-term impact on treating opiate dependence, it was a useful adjuvant in correcting acute precipitated opiate withdrawal [18].

In another clinical study by Krupitsky EM et al, seventy detoxified patients with heroin use disorder were randomly assigned to one of two groups receiving ketamine psychotherapy (KPT) involving two distinct doses of ketamine. The experimental group received existentially oriented psychotherapy along with a hallucinogenic ("psychedelic") dose of ketamine (2.0 mg/kg im), while the control group received the same psychotherapy combined with a low, non-hallucinogenic (non-psychedelic) dose of ketamine (0.2 mg/kg im). Both the psychotherapist and patient were unaware of the dose of ketamine. The therapy was comprised of preparation for the ketamine session, the ketamine session itself, and post-session psychotherapy focused on assisting patients incorporate the insights they gained from their ketamine session into everyday life. According to quantitative findings using the Hallucinogen Rating Scale, this double-blind, randomized clinical trial showed that patients who get a high dose of KPT (2.0 mg/kg) report having a full psychedelic experience. Conversely, low dose KPT (0.2 mg/kg) acts as ketamine-facilitated guided imagery and induces "sub-psychedelic" experiences. Also, high-dose KPT led to a significantly higher rate of abstinence in patients with heroin use disorder within the first two years of follow-up; a more pronounced and sustained decrease in heroin cravings, and greater positive changes in nonverbal unconscious emotional dispositions compared to low-dose KPT [19].

In a follow-up study, participants were 53 heroin-dependent patients who underwent single or three sessions (multiple) of ketamine-assisted psychotherapy (KAP), the multiple KAP group displayed a significantly higher abstinence rate of 50% compared to 22% for those who received only one session. However, there were no differences observed between the groups in terms of depression, anxiety, heroin cravings, or understanding of their life purpose [20].

4.3 Cocaine Use Disorder

According to a 2019 preclinical study, it was indicated that sub-anesthetic doses of ketamine enhance executive control networks, thereby

potentially reducing the impact of cocaine on decision-making. Ketamine infusion at these doses has also been shown to weaken the effects of acute cocaine use and significantly decrease cocaine-seeking behavior in rhesus monkeys [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 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 by a 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 cocaine use, 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].

5. 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. In a study conducted to evaluate the effects of the acute administration of sub-anesthetic doses of ketamine, both male and female Sprague-Dawley rats were used. The rats were trained to self-administer nicotine and were injected subcutaneously with 5, 7.5, and 10 mg/kg of ketamine or saline, and the impact on the quantity of intravenous nicotine infusions over a 45-minute session was recorded. The results showed that ketamine treatment substantially reduced nicotine self-administration in a dose-dependent manner. This study highlights the role of glutamatergic ionotropic receptors in addictive behaviors such as nicotine and alcohol use disorders and the modulation of these receptors could cause a reduction in nicotine dependence [24].

Cannabis use: A 6-week proof of concept study was conducted to evaluate the feasibility, tolerability, and potential therapeutic benefits of combining ketamine with a behavioral approach that included motivational enhancement therapy and mindfulness-based relapse prevention for treating cannabis use disorder. Eight individuals with cannabis use disorders participated, receiving either 0.71mg/kg or 0.41mg/kg ketamine infusions alongside the behavioral treatments. The study found that ketamine was well-tolerated without adverse effects, and it significantly reduced the frequency of cannabis use. Additionally, participants' confidence in their ability to abstain from cannabis in high-risk situations increased substantially from baseline to the study's end. These findings suggest that integrating ketamine with behavioral therapy is feasible, tolerable, and may be effective in treating cannabis use disorder [25].

6. SAFETY, TOLERABILITY, AND POTENTIAL ADVERSE EFFECTS

6.1 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. Improvements in obtaining access makes the intraosseous (io) route more efficient. The intramuscular (IM) route has been in use for a long time- it is safe and predictable, but painful during injection. Compared to the intravenous route (IV), the IM route is associated with a longer recovery time and a higher rate of vomiting. Ketamine has a poor oral bioavailability, but with small doses per os (PO), S- Ketamine can be used as an alternative for repeated intravenous infusions, especially in patients with chronic pain. Intranasal administration is another viable option, offering a rapid systemic absorption and convenient accessibility, which adds to its appeal. Ketamine should be titrated to the required clinical effect,

regardless of the route of administration [26]. Studies have shown that ketamine used at a subanaesthetic level is safe. The intravenous route is regarded the best route to control blood ketamine levels and is an established conventional route of administration for therapeutic purposes [14].

6.2 Adverse Effects

Ketamine 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 stimulates salivary secretions, potentially raising the risk of laryngospasm. This is likely caused by partial airway obstruction, which can typically be managed with basic airway maneuvers. So, it is advised to co-administer it 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. As an anesthetic, it can trigger various emergent phenomena, including sensations of floating, vivid pleasant dreams, nightmares, hallucinations, and delirium. These effects are more frequently observed in patients over 16 years old, females, those undergoing shorter surgeries, and when larger doses are administered rapidly [26].

6.3 Dissociative effects of ketamine

The most frequently reported psychoactive effect following the administration of a single subanesthetic dose of iv ketamine is dissociation, characterized by altered perceptions of visual, auditory, or sensory stimuli, as well as changes in the sense of self and time. Positive psychotomimetic effects can include disorganized thinking, hallucinations, paranoia, and unusual thought patterns. Negative psychotomimetic effects may involve flat affects, emotional withdrawal, and slowed movements. In a randomized, double-blinded, placebo-controlled trial conducted by Krystal et al. aimed to ascertain these effects, a 40-minute intravenous injection of ketamine at a subanesthetic dose of 0.5 mg/kg led to perceptual aberrations consistent with dissociative states. Also, positive and negative psychotomimetic effects were noted within 10 minutes of starting ketamine infusion and faded within 40 minutes after the treatment ended. In comparison, minimal to no psychoactive effects were noted at a dose of 0.1 mg/kg. [27]. As reported by some other studies, ketamine has also been demonstrated to worsen psychotic symptoms in patients with schizophrenia. Illusions and changes in hearing, vision, and body awareness have been observed with (S)-ketamine use, while the use of (R)-ketamine mainly causes feelings of relaxation [6].

Memory and Cognitive Impairment: In addition to the dissociative and psychotomimetic effects, several studies have identified the negative impact of the subanesthetic administration of ketamine on cognition. According to those studies, 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. Nevertheless, global cognitive function and immediate memory recall remain unaffected 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 [27]. Doses of ketamine used for recreational purposes may range from 1 and 2 mg/kg (intravenous), 50 and 150 mg (intramuscular), 100 and 500 mg (oral), or 30 and 400 mg (intranasal). At lower doses, users experienced mild stimulatory, dissociative, and hallucinogenic effects, while at higher doses, psychotomimetic symptoms and detachment from reality were observed [6].

The most common route of recreational administration is nasal 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 level of consciousness and sensory disconnection (referred to as K-hole), which some describe as equivalent to a near-death experience. At plasma concentrations between 50 and 200 ng/ml (0.21-0.84 μM), ketamine heightens sensory perception, such as intensified

sounds, while promoting emotional connectedness and experiences of unreality or depersonalization. Users have also reported side effects like dizziness, blurred vision, slurred speech, vomiting, palpitations, and chest pain. Prolonged ketamine use can lead to flashbacks, cognitive dysfunction, attention deficits, and reduced social engagement [6].

6.4 Emerging and Future Directions

Ketamine, in sublingual and intramuscular forms, has been used for decades by experienced psychotherapists in administering ketamine-assisted Therapy (KAT) [28]. Early addiction treatment trials employed high dosages of 2-3.0 mg/kg via intramuscular injection [20,28], but more recent research generally uses 0.41 mg/kg-0.71 mg/kg supplied intravenously, infused over 40-60 minutes [22].

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 substantial impact, increasing abstinence rates and decreasing the likelihood of alcohol use and heavy drinking as well as a longer time to relapse over 21 days after infusion, compared with midazolam. [29]. Similar results were replicated in heroin and cocaine use disorders when the KAP model was applied, where it showed abstinence, decreased craving, and lowered the time needed to relapse [19,23]. 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 in serum levels of BDNF neurotrophic factors being responsible for this impairment. The mechanism of action of ketamine's antidepressant properties 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.

7. 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 use disorders 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.

8. CONCLUSION

Substance use disorder is a public health concern globally, cutting across different age groups. Even though there is paucity 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.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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