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REVIEW
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Ketamine in Substance Use Disorder Treatment: A Narrative Review

ABSTRACT

Substance use disorder (SUD) continues to pose a significant global health challenge, necessitating innovative and effective therapeutic interventions. Ketamine, traditionally recognized for its anesthetic properties, has emerged as a novel and promising avenue for the treatment of SUD. This narrative review critically examines the current body of literature surrounding the use of ketamine in various forms and settings for individuals grappling with substance abuse. The review explores the neurobiological underpinnings of ketamine's potential therapeutic effects in SUD, shedding light on its impact on glutamatergic neurotransmission, neuroplasticity, and reward pathways. Special attention is given to the psychotropic and dissociative properties of ketamine, exploring their implications for both therapeutic outcomes and patient experience. Ultimately, this review aims to provide a comprehensive overview of the current state of knowledge regarding ketamine's role in the treatment of SUD, emphasizing the need for further research and clinical exploration. As we navigate the complex terrain of addiction medicine, understanding the nuances of ketamine's potential in SUD holds promise for the development of more effective and personalized therapeutic strategies.

Keywords: Alcohol dependence, ketamine, substance abuse

Introduction

Ketamine is an organic compound with pleiotropic effects on the body, its main mechanism of action is a noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptor. In addition to blocking nicotinic receptors,[1,2] it produces dopaminergic and serotonergic effects and is also a weak agonist of the delta and μ-opioid receptors.[1,2] As ketamine is very fat-soluble, it easily penetrates the blood–brain barrier, resulting in a very rapid effect on the central nervous system, which occurs after only about 5 minutes. Due to its short half-life of about 1-3 hours, its effect does not last very long.[3] It occurs in the form of 2 enantiomers: S and R. Ketamine is metabolized in the liver, where 4 metabolites are formed: hydroxynorketamine, dehydrononorketamine, hydroxyketamine, and norketamine. Ketamine is extensively metabolized, and caution should be exercised in individuals with renal or hepatic impairment as this may affect metabolism.[4] The metabolism of ketamine may also affect its own pharmacokinetics and the metabolism of other psychoactive substances such as opioids and cocaine.[5,6,7] It has been suggested that individual metabolism of ketamine may be a factor in predicting the response to the drug, highlighting the potential differences in metabolism between different individuals.[4] To date, it has mainly been used in medicine for preoperative anesthesia. It is an analgesic with a fairly safe effect profile and does not cause respiratory depression, which means that it does not require an oxygen supply. For this reason, it is the drug of choice for anesthesia in many developing countries. It is also one of the preferred anesthetics in emergency medicine. For some years now, ketamine has also been used in psychiatry. At the turn of the 20th and 21st centuries, the first double-blind studies were conducted on the efficacy of ketamine, particularly the S-enatiomer of ketamine, esketamine, in the treatment of drug-resistant depression.[8] Further studies confirmed these results and gave new hope for severely ill patients.[9,10,11,12] To date, the mechanism underlying the antidepressant effect of esketamine is not yet fully understood; however, the literature extensively documents the swift antidepressant efficacy of ketamine. Demonstrating rapid and sustained antidepressant effects

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in individuals with major depressive disorder (MDD) or treatment-resistant depression, ketamine exhibits response and remission rates ranging from 50% to 100% following a single administration.[13,14,15] The rapid onset of its antidepressant, antisuicidal, and anti-anhedonic actions positions ketamine as a promising treatment strategy for depression.[16] Additionally, ketamine has been proven to diminish suicidal ideation in depressed patients.[17] In comparison, esketamine, the enantiomer of ketamine, also displays antidepressant effects, albeit with a more prolonged duration than ketamine.[18,19] Studies indicate that the antidepressant effect of esketamine lasts from days to weeks, and it has obtained approval for treating resistant depression in the United States and Europe.[18] Research suggests that esketamine may be better tolerated than racemic ketamine while preserving antidepressant efficacy.[20,21] However, a direct comparison revealed that a higher percentage of patients exhibited an antidepressant response to racemic ketamine compared to esketamine at 1 week.[22] There are now also studies on its effectiveness in the treatment of addiction to psychoactive substances such as alcohol, heroin, and cocaine. Outside of medicine, it is also used for narcotic purposes. It belongs to the group of psychedelic dissociatives, which means that in doses lower than those used for anesthesia before surgery, it produces psychedelic experiences such as hallucinations, delusions, disorientation, and mystical experiences.[23-28] And at no higher doses, it can induce "near-death experiences" and "out-of-body" experiences".[27] Given the interesting pharmacological profile of ketamine, we, a group of psychiatrists with clinical and research experience in addiction treatment and in the delivery of intravenous ketamine treatment at a university clinic, with the support of students from our research club, decided to describe the potential use of the drug in addiction treatment. The articles used to summarize this text were selected on the basis of the authors' experience. They were searched in the PubMed publication database. Only articles in English were selected. As this review is a narrative review, the tools used in the preparation of systematic reviews, such as PRISMA, were not used.

Substance Use Disorder (Addiction)

Substance use disorder is a chronic and relapsing disorder of both physical and mental health characterized by a periodic or persistent compulsion to use a psychoactive substance, with tolerance to the previously consumed amount of the psychoactive substance increasing over time. The addict subordinates most of his activities to the addiction and neglects his professional, family, and private life. Stopping the use of the addictive substance leads to a subjectively unpleasant and potentially life-threatening abstinence syndrome. Diagnostic criteria can be found in both the International Classification of Diseases, Tenth Revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The problem of addiction affects many people. One of the most common addictions is alcohol dependence, which affects almost 5% of people worldwide.[29] The most important treatment for all types of addiction is currently all forms of psychotherapy – both individual and group therapy. Supportive pharmacological treatment is used, which includes substitution treatment, which aims to administer a substance that relieves the craving to use the substance but does not have pleasurable effects that may cause further development of the addiction. Treatment is also used to reduce the unpleasant effects of alcohol withdrawal. Despite numerous treatment methods, addiction remains a global problem that affects people from different social classes and causes suffering not only for the addicts themselves but also for those in their immediate environment. In addition, it is a major economic problem, as healthcare expenditure increases, the productivity of those affected by addiction decreases, and crime increases.[30] Despite the numerous treatment options available, the relapse rate within 1 year of starting addiction treatment ranges from 40% to as high as 80%.[31] Ketamine has the potential to increase the effectiveness of treatment and help many people return to a normal life.

MAIN POINTS

- *The review highlights ketamine, traditionally known for its anesthetic properties, as a novel and promising therapeutic intervention for individuals grappling with substance abuse, addressing the urgent global health challenge posed by SUD.*
- *The narrative review critically examines the current literature, delving into the neurobiological underpinnings of ketamine's potential therapeutic effects in SUD. It focuses on its impact on glutamatergic neurotransmission, neuroplasticity, and reward pathways, providing insights into the mechanisms that contribute to its effectiveness in treating substance abuse.*
- *Special attention is given to the psychotropic and dissociative properties of ketamine, exploring their implications for both therapeutic outcomes and patient experience. The review emphasizes the need for a comprehensive understanding of these properties in order to harness the full potential of ketamine as a treatment for SUD, underscoring the importance of further research and clinical exploration in addiction medicine.*

Ketamine in the Treatment of Addiction

There are few preclinical studies investigating the therapeutic properties of ketamine in the treatment of addiction. One study compared the effects of ketamine and memantine on alcohol and saccharin drinking.[32] Rats were given a choice between an ethanol solution, a saccharin solution, or a water solution. In this study, rats that preferred to consume ethanol were given the option of ingesting either the saccharin solution, ethanol, or water. After intraperitoneal administration of ketamine or memantine, the preference for the choice of beverage and the motor activity of the experimental rats were investigated. A dose of 20 mg/kg body weight significantly reduced ethanol intake in rats by up to 33%, compared to control group rats, and had no effect on locomotor activity or water consumption.

The first work looking at the effects of ketamine in the treatment of addiction in humans was conducted in Mexico in the 1970s. Salvador Rouqet administered the drug to humans and compared its efficacy to substances such as lysergic acid diethylamide (LSD).[33] However, the study could not be considered reliable. The researcher was eventually imprisoned. Reliable research results only emerged decades later from researchers Krupitsky and Grinenko, who published a scientific paper in 1997 describing their decades of experience studying the effect of ketamine on reducing relapse in alcohol-dependent individuals who had suffered alcohol intoxication in the near future.[34] In the Union of Soviet Socialist Republics (USSR), where these researchers worked, ketamine was used until it was banned by state authorities in 1998. Psychedelic ketamine therapy, as their treatment was called, consisted of 3 steps. The first step was preparation. It consisted of an initial psychotherapeutic session in which a qualified professional discussed with the patient what psychedelic

sensations they might experience. These experiences were designed to help patients become aware of the negative aspects of their addiction, including those related to their own identity and other issues in their personal life that stem from their addiction, and to embrace new values and find meaning in life. They were also made aware of the positive aspects of a sober life. The second step was the administration of ketamine. The substance was administered intramuscularly, and after administration, the therapist interacted with the patient. The therapist guided the patient through their own, often negative, experiences with the aim of making the patient reevaluate their life. For very strong sensations, patients were given the smell of alcohol. This was intended to evoke a negative association with the substance and further strengthen the desire for abstinence. In the final phase, group psychotherapy sessions were conducted in which patients discussed their experiences from the second phase with the help of a psychotherapist, with the session taking place the day after the administration of ketamine. In this way, sessions were conducted with about 1000 alcohol-dependent patients, with no adverse effects reported.[35] In their 1997 report, Krupitsky and Grinenko compared a group of patients treated with psychedelic ketamine therapy to a control group. Both groups underwent detoxification process prior to drug treatment. The research group was administered ketamine at a dose of 2.5 mg/kg body weight, while the control group underwent classic addiction therapy. It was found that only 24% of the patients in the control group remained abstinent 1 year after completing the detoxification treatment, while this percentage was 66% in the research group. Thus, the strong and positive effect of ketamine on the maintenance of alcohol abstinence was proven. However, the study had methodological flaws. It was not randomized or double-blind. Patients in the study group self-reported to the study, leading to varying levels of motivation to overcome addiction and a high willingness to undergo treatment with a novel medication, hence the high score. In addition, the control group did not receive a placebo and the content delivered to the groups differed significantly. This may have contributed to the very positive results of ketamine treatment. Grabski et al. (2022)[36] conducted a study from 2016 to 2019 in which they recruited participants through mass media, primary care, and addiction centers. Criteria included 24-hour abstinence, 0.00 parts per thousand on exhaled breath, and a goal of 6 months abstinence. Screening included medical history, physical and mental examinations, blood and urine tests, and an alcohol test. Participants (18-65 years old) suffered from alcohol problems, spoke English, and tested negative for most psychoactive substances. Exclusions included uncontrolled high blood pressure, certain medications, suicidal thoughts, and a specific psychiatric or substance use history.

Qualified participants were randomly assigned to 4 groups: Ketamine + therapy, ketamine + alcohol education, saline + therapy, and saline + alcohol education. Ten sessions were conducted, and alcohol consumption was tracked using timelines and diaries. A secure alcohol monitoring device was installed and later removed. Sessions were blinded, with therapists delivering both interventions. Ketamine infusions were given in sessions 2, 4, and 6 and lasted 40 minutes. The dose was 0.8 mg/kg, which was higher than in studies with antidepressants. The ketamine groups showed a higher percentage of abstinence for up to 24 weeks, with better results in the therapy + ketamine group. The placebo group showed fewer depressive symptoms after 3 months, which subsided after 6 months. Mild side effects were observed. Further research is needed, but the initial results suggest a promising role for ketamine in alcohol problems. Ketamine has also been studied in relation to the treatment of heroin addiction.[37] Krupitsky, who has also studied the effect of ketamine treatment on alcohol dependence, conducted a study on the effect of ketamine on heroin abstinence. This time, 70 heroin-dependent patients were randomly divided into 2 groups; the patients also underwent detoxification. They were divided into 2 groups, both of which received ketamine. One group received ketamine at a dose of 0.2 mg/kg body weight; this group was considered the control group. The other group received ketamine at a dose of 2.0 mg/kg body weight; this was the study group. Ketamine was administered intramuscularly in this study. After a follow-up period of 2 years, the abstinence rate was higher in the group that received higher doses of ketamine (17% in the group that received 2.0 mg/kg when compared to the group that received 0.2 mg/kg mc ketamine). In addition, a more sustained reduction in drug-seeking behavior was observed in the study group. The authors thus confirmed the dose-dependent effect of ketamine. Compared to the 1997 study, the current study provided more robust evidence due to the randomization and double-blind design. A weakness of this study is that the effect of ketamine was not compared with placebo, so it is not known whether both doses of ketamine are less effective than the inactive substance, although this is unlikely based on the previous positive results in achieving abstinence with ketamine. In 2007,[38] the same researcher compared the effect of one dose of ketamine with that of 3 doses of ketamine in combating relapse. The dose used at that time was 2.0 mg/kg body weight. Fifty-nine patients who had previously detoxified received a dose of ketamine. Six patients relapsed and were excluded from the further study. The remaining 53 patients were randomly divided into 2 groups. One group received 2 additional sessions of ketamine at monthly intervals. The other group also received one treatment session at monthly intervals. After 1 year, the abstinence rate was significantly higher in the group of patients who received 3 ketamine sessions. Half of the patients in the study group did not become addicted again, compared to 22% of the patients who had only received one dose of ketamine. This suggests that repeated doses of ketamine are more effective than a single dose. Both groups received psychological support. However, a weakness of this study was also the lack of a placebo in the control group. Nevertheless, the anti-addictive effect of ketamine in this patient group cannot be denied.

In 2014, a study was conducted with 8 people with low motivation to quit cocaine addiction who received 3 doses of ketamine 48 hours apart.[39] The study was double blind. The control group received 2 mg lorazepam, while the study group received ketamine at a dose of 0.41 mg/kg body weight or 0.71 mg/kg body weight. Compared to the group receiving lorazepam, the motivation of the men in the study group increased. The effect was greater in those who received higher doses of ketamine. Patients showed a reduction in the amount and frequency of cocaine use within 4 weeks of the study compared to baseline. However, this study was only conducted with a small group, and no placebo was used. In another study, the same research group investigated the effect of a single dose of ketamine administration in 20 ketamine-dependent participants with no depressive symptoms and no motivation for drug treatment.[40] The study was double-blind and randomized, and the entire study lasted 2 weeks. Patients were administered midazolam at a dose of 0.025 mg/kg body weight or

ketamine at a dose of 0.71 mg/kg body weight. The aim of the study was to test the frequency of self-reported cocaine use. The study group reduced cocaine use by 67% compared to patients taking midazolam. In addition, ketamine significantly reduced drug craving. Within the first 3 days, patients treated with ketamine significantly reduced their ketamine use, and some remained abstinent throughout the 2-week study.

Although ketamine is not yet established in the treatment of addiction, there are doctors who have successfully used it in addiction treatment. In the United States, it has been used in clinics since 1994, not only for treating addiction to psychoactive substances but also for behavioral addictions such as binge eating. Anecdotal evidence has generated high hopes for its efficacy.[42,42]

Furthermore, the potential for enhancing the effectiveness of ketamine in treating addictive disorders has been directly suggested through psychological interventions. Jones et al. proposed that the impact of ketamine could be heightened when combined with cognitive-behavioral psychotherapy, indicating a possible synergy between psychological interventions and ketamine in addressing addictive disorders.[43] This well-founded study implies that the amalgamation of ketamine and psychological interventions shows promise in the treatment of addictive disorders.

Possible Mechanism of the Therapeutic Effect of Ketamine in the Treatment of Addiction

One possible mechanism by which ketamine contributes to the maintenance of abstinence is its positive effects on synaptogenesis. Decreased neuroplasticity and reduced glutamatergic transmission are thought to be associated with addiction.[44,45] Ketamine most likely influences synaptogenesis through NMDA receptor antagonism, leading to the synthesis of relevant proteins and the insertion of α-amino-3-hydroxy-5-methyl-4-isoxazolepropioni (AMPA) receptors,[46] therefore, ketamine reverses the changes in glutamatergic transmission that occur in addiction and depression. Interestingly, administration of rapamycin (an mammalian target of rapamycin [mTOR] antagonist) reduces both the addictive[32] and antidepressant effects of ketamine,[46] suggesting that both effects may be due to enhanced neuroplasticity by ketamine. Further studies have shown that mTOR signaling is enhanced by ketamine metabolites *in vivo* and *in vitro*.[47] However, other studies cast doubt on the above mechanism. Zanos et al. (2016) investigated the effect of one of the ketamine metabolites (2R,6R)-hydroxynorketamine in a forced swim test and a learned helplessness test in mice.[48] They evaluated its effects on NMDA and AMPA currents in the hippocampal slices of the tested mice, as well as the expression of mTOR, Brain-derived neurotrophic factor (BDNF) and GluA1-2, concluding that the tested metabolite is not active in the NMDR but still exerts antidepressant effects, albeit at different levels than mTOR. Therefore, further studies are needed to evaluate the relationship between the effects on synaptogenesis and the antidepressant effects. The possible mechanism is to increase neuroplasticity, particularly in the hippocampus and cortex, which contributes to the maintenance of abstinence to reduce the risk of self-administration and susceptibility to relapse.[49,50] Reduced neurogenesis may also be associated with a decrease in BDNF. A study[51] examining BDNF levels in 37 alcohol abusers showed reduced BDNF levels. A similar reduction in BDNF levels was observed in another study of heroin and cocaine addicts; furthermore, levels appeared to return to preaddiction levels during treatment.[52,53,54] Mice with a knockout mutation in the BDNF gene show no antidepressant response to ketamine,[55] with a similar effect when anti-BDNF antibodies are administered.[56] In addition, individuals who respond well to ketamine when it is used to treat depression have been shown to have increased levels of BDNF in their plasma, while no such phenomenon has been observed in individuals who do not respond.[57] The increase in BDNF is closely related to the antidepressant effect of ketamine.[57] However, in one study, no increase in BDNF was observed even up to 4 hours after ketamine administration,[58] furthermore, the effect of ketamine on BDNF may be age-dependent.[59,60]

It has been suggested that although ketamine elicits strong dopamine transients In the nucleus accumbens, it does not trigger the synaptic plasticity typically associated with addictive drugs in mice. However, ketamine supports the reinforcing effect by disinhibiting dopamine neurons in the ventral tegmental area (VTA). This reinforcing effect is favored by N-methyl-D-aspartate receptor (NMDAR) antagonism in GABA (γ-aminobutyric acid) neurons of the VTA but is rapidly terminated by type 2 dopamine receptors on dopamine neurons. The rapid termination of dopamine transients in conjunction with NMDAR antagonism prevents the induction of synaptic plasticity in both the VTA and the nucleus accumbens. Importantly, this dual action of ketamine does not lead to locomotor sensitization or uncontrolled self-administration, resulting in a unique constellation of dopamine-driven positive reinforcement with low risk of addiction.[61]

Although narrative overviews offer a comprehensive synthesis of the existing literature, they are subject to certain limitations. First, there is the possibility of bias in the selection of studies, as narrative reviews often rely on the subjective judgment of the author. In addition, there may be a lack of systematic and transparent methodology, which can affect the reproducibility and objectivity of the review process. In contrast to systematic reviews, narrative reviews may not use rigorous search strategies or standardized criteria for inclusion and exclusion, which can lead to a selective presentation of the literature. In addition, the lack of statistical analysis in narrative reviews limits the ability to quantify and compare the effect sizes of different studies. Despite these limitations, narrative reviews are still valuable in providing context, hypothesizing, and providing insights into the existing knowledge landscape.

Conclusion

Previous studies provide promising results for improving addiction treatment. The results presented show that ketamine can be useful not only in the treatment of alcohol addiction, but also heroin and cocaine addiction. It can also reduce drug cravings. However, these studies have limitations, so further high-quality studies with a larger group of people are needed for ketamine to be included in the standards for the pharmacological treatment of addiction. In addition, the mechanism of action of ketamine that contributes to the maintenance of abstinence is not yet fully understood. Various therapeutic interactions need to be studied in combination with ketamine to determine the best treatment regimen for addicts. Furthermore, it is important to de-taboo the use of ketamine among both healthcare professionals and patients themselves.

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