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Subanesthetic ketamine for reducing the harm of cocaine use disorder

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Abstract

Subanesthetic ketamine offers promising potential for reducing harm in individuals with cocaine use disorder (CUD). Research indicates that even a single dose can lessen cravings and decrease drug-seeking behaviors, though achieving long-term abstinence remains challenging. However, reduced cocaine consumption itself is a meaningful outcome. Ketamine's potential in reducing the harm of CUD is also supported by its mechanism of action in the dopaminergic system, as it counters cocaine's effect by interacting with dopamine receptors, stabilizing brain-derived neurotrophic factor levels, and modulating lateral habenula neuron bursting. In addition, concerns about ketamine's abuse potential are minimized when it is administered in a clinical setting under professional supervision. This is supported by its success as a treatment for depression, indicating that, with appropriate safeguards, ketamine could be a valuable pharmacological strategy for harm reduction in CUD. When developing ketamine as a CUD harm-reduction strategy, it is also important to account for sex differences, which may affect patients' sensitivity to ketamine and the potential for misuse. Although the promising effects of ketamine in treating depression support its use for CUD, most studies have focused on depression models, and additional research is needed to confirm safety and understand its specific mechanisms in CUD. Nonetheless, subanesthetic ketamine is a promising CUD intervention and should be further explored to provide an efficient and safe solution for patients in need. This narrative review mainly elucidates the ongoing research regarding ketamine's mechanisms of action, pharmacology, and clinical application potential in CUD.

Keywords: Cocaine use disorder; Ketamine; Dopamine; Nucleus accumbens; Ventral tegmental area; N-methyl-D-aspartate receptor; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Brain-derived neurotrophic factor

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1. Introduction

Cocaine, the second most used illicit drug worldwide, remains a significant public health concern.[1] According to the United Nations Office on Drugs and Crime, in 2020, the number of past-year cocaine users reached over 20 million worldwide.[2] Like other substance use disorders, cocaine use disorder (CUD) is a chronic condition represented

by an inability to control drug seeking and intake despite damaging consequences.[3] The addictive property of cocaine is associated with its ability to interact with the mesolimbic pathway (Figure 1). This pathway includes the ventral tegmental area (VTA) innervating the ventral striatum, which includes nucleus accumbens (NAc), an area important for forming and maintaining addiction-related memory and contributes to relapse.[4] Most NAc neurons are medium spiny neurons (MSN), which are γ-aminobutyric acid (GABA)ergic neurons classified by the type of dopamine receptors they express. Although signaling pathways of these two types of neurons are highly complex, MSNs that express type 1 dopamine receptors (D1-MSN) are classically associated with rewards.[5-7] MSNs that express type 2 dopamine receptors (D2-MSN) can lead to decreased motivation and locomotion[8,9] (Figure 1).

Cocaine interacts with the mesolimbic pathway by remodeling glutamatergic synapses, especially those in D1-MSN,[10-12] creating "silent synapses," which are immature glutamatergic synapses that contain N-methyl-D-aspartate receptors (NMDAR) but not α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR).[13] NMDAR is a glutamate-gated calcium channel that activates when AMPAR-induced depolarization displaces a magnesium ion blocking it (Figure 2). Lacking AMPARs, these "silent synapses" cannot be activated and thus are not considered mature.[14,15] During cocaine withdrawal, these synapses mature quickly by recruiting AMPARs, leading to depolarization, NMDAR opening, calcium ion release, and eventually long-term potentiation, thus promoting addiction.[12]

Despite decades of research, most treatments for CUD rely on psychosocial interventions as there are currently no Food and Drug Administration (FDA)-approved pharmacological treatments.[1] However, ketamine, a non-competitive NMDAR antagonist, has gained attention as a promising pharmacological treatment for CUD. Ketamine is a racemic mixture of two enantiomers, S and R ketamine, with the S enantiomer (esketamine) being more potent. While ketamine has been used as a general anesthetic due to its dissociative effects, a subanesthetic dose of esketamine has been approved to treat depression[16] Although ketamine has a history of misuse as a recreational drug,[17,18] no overdose or fatality has been reported when it is used in a therapeutic setting.[18,19] Recently, due to ketamine's antagonistic effect and the association between depression and substance use disorders, there has been a lot of interest in exploring its therapeutic potential in treating various types of addictions.[20]

In this narrative review, we summarize the evidence presented in both pre-clinical and clinical studies illustrating ketamine's effect in reducing cue-induced

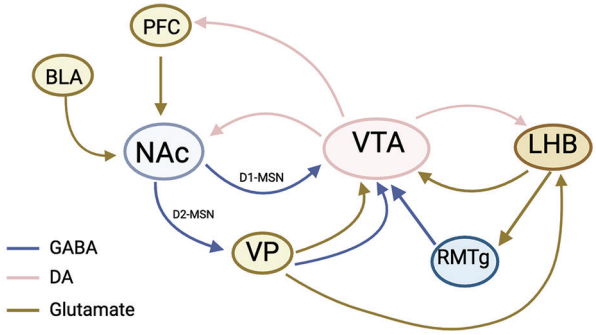


Figure 1. The brain circuits involved in cocaine use disorder prominently feature the ventral tegmental area (VTA), which plays a critical role in motivation, sending dopaminergic projections to the prefrontal cortex (PFC), nucleus accumbens (NAc), and lateral habenula (LHB). The NAc, a vital hub in this network, receives glutamatergic inputs from areas such as the PFC and basolateral amygdala (BLA). Subsequently, the NAc can project GABAergic signals directly to the VTA or indirectly through the ventral pallidum (VP). The direct pathway enhances cocaine-related conditioning, whereas the indirect pathway serves to inhibit it. Recent research suggests that both pathways can influence either reward or aversion, depending on the stimulation patterns.[6] In addition, the LHB sends direct excitatory projections to the VTA but can also inhibit VTA dopaminergic neurons by activating the rostromedial tegmental nucleus, which in turn delivers GABAergic signals to the VTA.[64,122]
Abbreviations: DA: Dopamine; GABA: γ-aminobutyric acid; MSN: Medium spiny neuron.

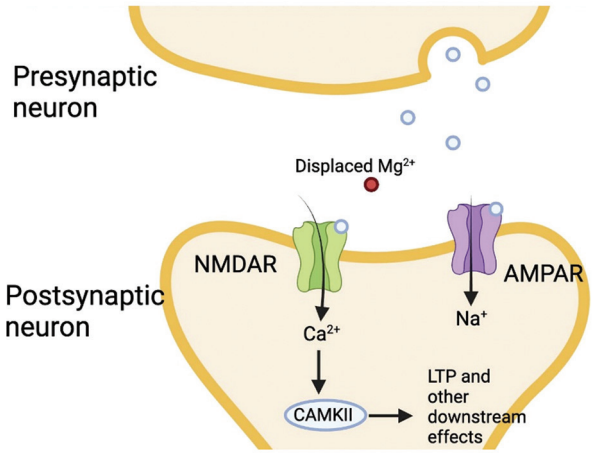


Figure 2. The intricate workings of NMDAR and AMPAR on post-synaptic neurons. These two glutamate-gated ion channels, which allow sodium or calcium to flow through when glutamate binds, are a testament to the complexity of neuroscience. NMDAR, with its slower kinetic than AMPAR's due to magnesium ion blockage, is a fascinating subject of study. Its activation can lead to downstream effects such as long-term potentiation or depression through calcium ion activation of targets like CAMKII.[123]
Abbreviations: AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CAMKII: Calcium/calmodulin-dependent protein kinase II; LTP: Long-term potentiation; NMDAR: N-methyl-D-aspartate receptor.

craving and drug-seeking behaviors in cocaine users while acknowledging its potential for misuse. In addition, we review ketamine's potential mechanisms and sex-dependent differences in ketamine's therapeutic effect. Finally, we identify a barrier to developing interventions for cocaine abuse as the expectation of abstinence. Grounding the approval standards for pharmacological interventions on more realistic patient-centered outcomes[21] would allow for the repurposing of ketamine as an efficacious harm-reduction medication for CUD.

2. Pre-clinical studies on ketamine's effectiveness in reducing cocaine use

In pre-clinical settings, subanesthetic ketamine can decrease cue-induced drug-seeking behaviors and lead to changes in brain connectivity associated with increased executive control. Fitzpatrick and Morrow[22] conducted a study using a Pavlovian-conditioned approach to investigate the effect of subanesthetic ketamine in rats, focusing on two behaviors: sign-tracking and goal-tracking. Sign tracker rats, who attribute motivation incentives to reward cues, display increased drug-seeking behavior, whereas goal tracker rats do not model addictive behavior. Subanesthetic ketamine at 32 mg/kg dose decreased sign-tracking behavior in sign-trackers without affecting goal-tracking behavior in goal-trackers, with effects lasting up to 48 h post-administration.[22] This indicates that a subanesthetic dose of ketamine reduced reward-seeking behaviors in the rats that were most vulnerable to impaired executive function related to addiction. Similarly, a study on cocaine-exposed rhesus monkeys evaluated the effects of subanesthetic ketamine on functional brain connectivity and cocaine self-administration.[19] Ketamine treatment at 48 h before cocaine self-administration reduced the cocaine-induced decrease of functional brain connectivity between brain regions involved in decision-making and reward processing. A separate cohort of cocaine-exposed rhesus monkeys exhibited reduced drug- and cue-induced reinstatement following subanesthetic ketamine.[19] These findings demonstrate ketamine's ability to decrease drug intake by modulating the interaction between different brain areas.

3. Clinical studies on ketamine's effectiveness in reducing cocaine use

Although clinical studies provide relevant models of substance abuse behaviors, their findings may not always translate directly to human subjects. Nonetheless, many clinical research results were consistent with that of the pre-clinical studies. In an observational study, Gao *et al.*[23] used artificial intelligence, validated by specialists, to identify ketamine as the best candidate for reducing the harm of CUD. They then assessed ketamine's therapeutic effects retrospectively using data from a de-identified patient database. Compared to cohorts who received other antidepressants or anesthesia medications, cohorts that received ketamine had a higher CUD remission rate.[23] Prospective clinical studies also support subanesthetic ketamine's effectiveness in decreasing craving and drug-seeking behaviors. In a 2013 clinical trial, Dakwar *et al.*[24] evaluated the effect of subanesthetic ketamine in eight non-treatment-seeking cocaine-dependent participants. A single ketamine infusion significantly increased motivation to quit and reduced cue-induced craving, demonstrating ketamine's potential to motivate behavioral change. The same investigators later explored whether a single subanesthetic dose of ketamine could disrupt cocaine self-administration in a cohort of 20 cocaine-dependent individuals disinterested in abstinence.[25] After infusions of subanesthetic doses of ketamine, participants chose between immediate cocaine self-administration and delayed monetary rewards. Remarkably, a single ketamine dose also significantly decreased cocaine self-administration. A hallmark feature of substance use disorders is a persistent desire to use the drug such that it becomes the only goal of the affected individual's life.[1] The fact that a single subanesthetic dose of ketamine enabled non-treatment-seeking subjects to choose money over cocaine is a testament to ketamine's potential as a CUD harm-reduction therapy.

4. Abuse potential of ketamine

Due to its history of recreational misuse, ketamine as a treatment for CUD may raise concerns about abuse potential and adverse effects.[26] Ketamine use for recreational purposes has increased in recent years, as reflected by a significant rise in ketamine-related seizures from 2012 to 2019.[27] However, ketamine differs from substances such as cocaine in that ketamine does not modulate synaptic plasticity in the same way.[28] Both clinical and pre-clinical studies suggest low abuse potential at subanesthetic doses of ketamine. For instance, a study found that daily ketamine doses of 2.5 and 5 mg/kg over 6 days failed to evoke a conditioned place preference in rats.[29] In addition, although the S enantiomer of ketamine has a more substantial behavioral effect and is responsible for ketamine's abuse potential,[30,31] most clinical trials use a racemic mixture of ketamine to improve CUD outcomes. Because substance abuse is greatly context-dependent, when subanesthetic ketamine is administered in professionally controlled settings, ketamine's abuse risk is minimized by effective monitoring and administration

in medical contexts.[19,26] Dakwar *et al.*[24] reported that high and low subanesthetic doses of ketamine could be safely given under controlled conditions to participants with CUD who do not engage in ketamine misuse. In addition, the repurposing of subanesthetic ketamine for treatment-resistant depression (TRD) illustrates the feasibility of employing ketamine as a CUD intervention. The nasal spray Spravato, composed of the S-ketamine enantiomer, was approved by the FDA as a treatment for TRD in 2019.[32] Spravato is accessible through a controlled distribution program in the United States and Canada, which requires direct supervision and monitoring by a certified health-care professional for at least 2 h post-dose.[26] The same distribution model can be utilized for the treatment of CUD with subanesthetic ketamine to ensure cocaine-dependent individuals can safely receive medical care.

Although research shows that administering subanesthetic doses of ketamine should be safe in clinical settings, ketamine misuse can still cause unpleasant side effects and pose health risks.[33] Ten to twenty percent of ketamine users experience the emergence phenomenon, which is a collection of symptoms including hallucinations, delirium, euphoria, and paucity of speech.[33] Ketamine can also cause changes in heart rate and blood pressure, posing risks for users with a history of myocardial infarction or hypertension.[33] Nonetheless, the side effects of ketamine are both a curse and a blessing when considering its potential as a pharmacotherapy. Subanesthetic doses of ketamine might also cause a range of psychoactive effects, some of which might appear like "spiritual" experiences. They might assist in individuals' transition from one lifestyle to another guided by ethical values.[34] Dakwar *et al.*[35] performed two more clinical trials to investigate whether these effects contribute to the decrease in cocaine-seeking behavior. In 2014, the group recruited eight participants with CUD. The exposure group received two ketamine infusions of different doses separated by 48 h, and another group received the positive control lorazepam.[35] In a 2019 follow-up study, the researchers examined 20 participants over three 6-day hospitalization sessions. Participants received either ketamine or positive control during the second and third hospitalization sessions. Both studies found that mystical effects mediated ketamine's effectiveness in reducing cocaine-seeking behavior, though the 2019 study also noted that these effects might reflect individual sensitivity to ketamine rather than its therapeutic impact alone.[36] Thus, some of ketamine's psychiatric side effects of ketamine might even be the underlying mechanism of its ability to improve CUD remission.

5. Potential mechanisms behind ketamine's harm-reduction effect

Despite the clinical and pre-clinical evidence pointing to ketamine's potential in care for CUD, the mechanisms behind its therapeutic effects remain contentious. One possible mechanism might be implicated in ketamine's effectiveness in treating depression, as clinical studies have been investigating anti-depressants' potential in treating substance use disorder.[23,37] The co-occurrence of major depressive disorder (MDD) and substance abuse is common,[38,39] and cocaine use itself can also induce depression during periods of heavy drug use.[40,41]

In addition, studies find that both cocaine-induced depression and independent MDD are associated with substance use relapse in both rats and humans.[41,42] Thus, this bidirectional relationship – where cocaine can trigger depression, and depression can hinder remission from use – underscores the importance of addressing both conditions simultaneously. Given that depression, CUD, and ketamine all modulate overlapping neurological pathways, ketamine may be particularly well-suited for treating CUD by targeting these shared mechanisms.

5.1. Ketamine directly modulates the dopaminergic system

One possible mechanism is that ketamine modulates the monoamine systems that are involved in both cocaine addiction and depression. Cocaine withdrawal often triggers depressive symptoms, which, unlike MDD, temporarily improve with cocaine use and respond poorly to selective serotonin reuptake inhibitors.[43] The association between cocaine and depression is due to cocaine's mechanism of action. Cocaine works by binding to the dopamine transporters (DAT) responsible for the reuptake of dopamine and by upregulating D1 dopamine receptors (D1Rs), which have stimulatory effects and are often involved in compulsive drug intake.[44,45] Both actions can lead to an increase in dopamine signaling.[46]

When cocaine use stops, there is an acute decrease in striatal dopamine levels[47] and a reduction of dopamine receptor 2 (D2R) signaling in the ventral striatum due to reduced D2R sensitivity.[48] Such reduction is also seen in independent depressive disorder, which is associated with a decrease in several monoamines, including serotonin and dopamine.[49] In addition, long-term cocaine users will develop tolerance, leading to increased DAT density and reduced dopaminergic (DAergic) signaling,[48,50] thereby reinforcing cocaine use.

Ketamine, which also affects the DAergic system, may potentially reverse cocaine's effect. Studies found that

ketamine increases the firing rate of DAergic neurons in the VTA for up to 24 h post-injection,[51] potentially due to its ability to activate D1R[52,53] by inhibiting several microRNAs in the medial prefrontal cortex (mPFC).[54,55] This can correct the low dopamine level and depressive symptoms seen during cocaine withdrawal, as activating D1R contributes to ketamine's antidepressant effect by promoting spinogenesis and dendritic plasticity.[55] Consistent with this finding, ketamine-induced behavior sensitization is abolished by a D2R antagonist, suggesting ketamine may activate D2R as well.[56] This supports ketamine's treatment potential for CUD, as the activation of D2-MSN in NAc suppresses cocaine self-administration.[8,57]

Interestingly, another study found that neither ketamine nor its metabolite showed any antagonist/agonist effect on D1R or D2R. Instead, ketamine's effect on dopamine is mediated by its effect on AMPA and NMDA receptors on VTA DAergic neurons.[9,58] It has been shown that acute ketamine administration increases DAergic neuron firing by amplifying AMPA transmission, whereas AMPAR antagonists abolish this effect.[59,60] Consistently, chronic ketamine administration led to an increase in AMPAR but not NMDAR density, pointing to ketamine's direct impact on AMPARs.[60]

Despite ketamine's therapeutic potential, there is still concern about its abuse risk, especially as it activates D1R, increases DAergic neuron activity, and inhibits DAT similarly to cocaine.[61-63] However, ketamine does not induce the same drug-evoked synaptic plasticity, especially at a subanesthetic dose. This is because synaptic plasticity generally requires NMDAR activation for excitatory synapse potentiation onto VTA DAergic neurons, while ketamine blocks NMDARs. In addition, ketamine's fast off-kinetic profile prevents prolonged dopamine increases that would otherwise promote synaptic plasticity.[28] Thus, despite its similarity with other addictive substances, ketamine's mechanism of action suggests a lower abuse potential. Nonetheless, more research needs to be done to elucidate the best method to take advantage of ketamine's therapeutic effect in clinical settings.

5.2. Ketamine modulates lateral habenula (LHb) neuron bursting

Another mechanism through which ketamine can alleviate depressive symptoms is by blocking neuronal bursting activity in the LHb. The LHb is associated with negative reward processing, as it stimulates the rostromedial tegmental nucleus, which inhibits VTA DAergic neurons (Figure 1).[64] Based on their activity, LHb neurons could be categorized as: silent, tonic-firing, and burst-firing.[65] Several studies found that, in animal models of depression, potassium channels in astrocytes near LHb are upregulated, leading to hyperpolarization. This change in membrane potential can lead to LHb bursting, a pattern dependent on the activation of NMDAR.[66,67] This type of bursting increases the likelihood that action potentials will reach the downstream synaptic target, thus enhancing the inhibitory effect of LHb on midbrain DAergic neurons.[68]

In a mouse model, optogenetically inducing this bursting pattern in LHb neurons can lead to depressive-like symptoms whereas blocking NMDAR rescued depressive-like symptoms.[64] Consistent with these findings, Ma *et al.*[69] reported that systemic ketamine injection significantly reduced bursting neurons in mice brain slices just 1-h post-injection, with effects lasting up to 24 h. Although these studies are mostly done using depression models, cocaine's ability to induce depressive symptoms through similar pathways underscores ketamine's potential in treating CUD. A study found that cocaine administration increased the phosphorylation at S845 of GluA1, a subunit of AMPAR in the LHb.[70] Phosphorylation at this position can increase AMPAR insertion on the cell surface and the probability of channel opening, thus increasing the chance of NMDAR activation.[71] Interestingly, although blocking AMPAR did not decrease burst firing in LHb neurons, increased AMPAR current or administration of AMPA increased burst frequency.[66] These findings suggest that cocaine may cause depressive symptoms by trafficking AMPARs to cell membranes, thus increasing LHb neuron bursting activity. Ketamine can then target this process by blocking the downstream NMDAR to stop the bursting of LHb neurons, thus assisting in CUD remission. These studies demonstrate that ketamine may reverse the depressive symptoms associated with CUD by preventing LHb bursting.

5.3. Ketamine modulates brain-derived neurotrophic factor (BDNF) levels

A third mechanism by which ketamine may aid in CUD treatment is through its modulation of the BDNF level, the most abundant neurotrophic factor in the nervous system. By binding to its receptor tropomyosin kinase B (TrkB), BDNF can modulate addiction-related neuronal plasticity.[72] Cocaine's effect on BDNF varies depending on the stage of the addiction cycle.[73,74] Research indicates that serum or plasma BDNF levels increase with acute cocaine use and during periods of cocaine abstinence but decrease with prolonged cocaine use.[75-79] This is consistent with the co-occurrence between cocaine use and depression since a decrease in BDNF is also associated with depression.[80] Interestingly, during withdrawal, a high level of BDNF is associated with cocaine craving, and cocaine-induced depression has a higher BDNF level compared to primary

MDD.[77,81,82] Thus, instead of consistently up- or down-regulating BDNF, cocaine appears to cause fluctuation in BDNF levels that contribute to the addiction.[74]

Consistent with ketamine's interaction with the mesolimbic system, ketamine can also modulate BDNF, which, along with TrkB, is expressed in the VTA-NAc circuit.[83] Several studies found that ketamine can increase BDNF expression in various brain areas, an effect that can last up to 30 days after a single infusion of ketamine.[84,85] In clinical studies, higher plasma BDNF level is associated with the anti-depressant effect of ketamine in patients.[86,87] Other studies also directly demonstrated BDNF's effectiveness in reducing cocaine consumption, as pre-clinical research shows that a single injection of BDNF to the dorsomedial prefrontal cortex and NAc can decrease cocaine-seeking behavior.[88] Notably, such effect is specific to cocaine and no other natural awards such as sucrose solution.[87,88] Together, this evidence suggests that ketamine might facilitate CUD treatment by stabilizing the BNDF level. Nonetheless, studies that specifically explore this relationship should be conducted.

One limitation of the clinical studies mentioned above is that most measured plasma BDNF as a proxy for brain BDNF levels. This is because BDNF crosses the blood–brain barrier easily, and there is a high correlation between plasma and cerebral spinal fluid concentration in BDNF.76 However, BDNF's effects vary across brain regions. For example, increased VTA BDNF expression enhances cocaine seeking, but injection into the dorsomedial prefrontal cortex attenuates CUD relapse.[89,90] Thus, while plasma or serum BDNF is the best choice for clinical studies, pre-clinical studies can further elucidate the brain area where BDNF acts to facilitate ketamine's therapeutic effect on CUD.

6. Sex differences in response to ketamine

While plenty of evidence illustrates ketamine's potential effectiveness in treating CUD, pre-clinical studies also suggest that there might be a difference in ketamine's harm-reduction effect in males versus females. For instance, ketamine rescued social isolation-induced decreases in mPFC spine density in male but not female rats.[91] In addition, continuous administration of a subanesthetic dose of ketamine resulted in antidepressant effects in male rats but anxiety- and depressive-like behavior in female rats.[92]

6.1. Which hormones are responsible for these sex-dependent differences?

Although evidence points to a sex-dependent response to ketamine, studies differ on which sex hormone causes this difference. Multiple pre-clinical studies showed that females are more sensitive to ketamine at a lower dose,[93] and its effect is estrogen-dependent but not testosterone-dependent.[94] For instance, in response to ketamine, there is a significant increase in BDNF levels in female depressed rats compared to male ones.[95] Specifically, proestrus, but not diestrus, female C57BL/6 mice exhibited enhanced sensitivity to a very low dose of ketamine (1.5 mg/kg), possibly due to estradiol's effect on synaptic plasticity.[96] These studies seem to point to estrogen as the reason behind females' heightened sensitivity to ketamine.

However, several other studies that investigated the pharmacokinetics of ketamine found the male hormones to be responsible for the sex-dependent differences. Highland *et al.*[97] found that, compared to male rats, female CD-1 rats have a higher plasma level of a ketamine metabolite at 10 and 30 min after ketamine injection. This metabolite, hydroxynorketamine, is responsible for the antidepressant effect of ketamine. On the other hand, male rats have a higher plasma level of unmetabolized ketamine. While ovariectomy did not eliminate the difference between female and male ketamine metabolism, orchidectomy did, suggesting that testosterone may play a role in ketamine metabolism.[97] This is inconsistent with another study by Saland *et al.*,94 which found that female Sprague-Dawley rats have higher ketamine plasma levels 30 min post-injection. Yet, since Saland *et al.*[94] did not find a difference between proestrus and postestrus rats, both studies agreed that female hormones do not play a role in the sex-dependent difference in ketamine pharmacokinetics. In addition, studies found that ketamine might exert its effect partially through interacting with mu-opioid receptors, and this effect was only significant in male rats.[98,99] This opioid-dependent effect is reversed by orchiectomy, suggesting that testosterone plays a role in the ketamine effect.[98] This is consistent with a study that showed concurrently administering naltrexone, a mu-opioid receptor antagonist, with ketamine in a female human subject did not block ketamine effects.[100] Thus, these studies suggest that testosterone could either be driving the observed sex differences in ketamine sensitivity or that males are more sensitive to ketamine, directly opposing the studies mentioned in the previous paragraph.

6.2. Sex- and age-dependent differences in ketamine's abuse potential

In addition to its therapeutic effect, ketamine's abuse potential may also be sex-dependent. A study found that female rats exhibit higher locomotor sensitization to repeated antidepressant doses of ketamine,[33] with this effect occurring at a lower dose in female rats than in male rats.[101] Locomotor sensitization is the increased

behavioral response in rodents to repeated exposure to psychostimulant drugs, and it shares features with addiction in humans.[102,103] Thus, these studies suggest that females are at a higher risk of ketamine abuse compared to males.

However, studies have also shown that, at a higher dose (20 mg/kg), ketamine administration in juvenile male rats increased the preference for cocaine during adulthood. This effect was not observed in female rats at any age, suggesting that males might be at a higher risk for ketamine-related drug abuse potential.[104] Another study investigating ketamine's abuse potential at 80 mg/kg found female Sprague-Dawley rats across all ages produced high locomotor activity, whereas only preweaning male Sprague-Dawley rats showed a similar response, with adult and adolescent males displaying less activity.[105]

One reason for the discrepancy in research results might be that different strains of rats may respond differently to ketamine.[106] Taken together, these results suggest that both age and sex need to be considered when exploring ketamine's potential side effects.

6.3. Implication for developing ketamine as CUD harm-reduction strategy

The pre-clinical research results mentioned above highlight the importance of continuing to explore the sex-dependent effect of ketamine. This is especially important since cocaine addiction is also sex-dependent, with females being more likely to progress through the addiction cycle, and cocaine-seeking behavior correlates with female sex hormone levels.[107,108] However, it is also important to recognize that the biological differences between humans and rats may render pre-clinical research results less beneficial when developing ketamine as a treatment.

Clinical research did not seem to find that humans exhibit sex-dependent responses to ketamine. One clinical study that investigated ketamine's antidepressant effect found that, although there was no significant difference in ketamine's treatment response in males versus females, females reported more headache and nausea as ketamine's side effect. However, the difference between the male versus female side effects was not significant.[109] In addition, a 2022 systematic review of 27 clinical studies published from 2012 to 2020 found no significant sex difference in response to ketamine treatment.[110]

The discrepancy between the conclusions of the rat and human studies might be due to the size limitation in most clinical trials. While the biological differences between rats and humans should not be overlooked, there is a need for larger trial clinical studies exploring how sex hormones influence response to ketamine therapy in humans. In addition, since most studies of ketamine explore its antidepressant effect, it would be beneficial to specifically study female versus male responses to ketamine's therapeutic effect on CUD.

7. Abstinence or use reduction as primary goal of pharmaceutical intervention of CUD

While evidence suggests that ketamine may reduce cocaine use, research on whether subanesthetic ketamine can lead to long-term abstinence generated mixed results. Dakwar *et al.*[24] measured cocaine use behavior a month after ketamine treatment and found that a mere two of the eight participants achieved urine-confirmed abstinence at follow-up. However, the same group performed a more extensive study with 55 patients who received a single ketamine infusion or midazolam during 5 days of hospitalization. Each participant also attended daily sessions of mindfulness-based relapse prevention (MBRP).[111] After the 1st week, the participants received 4 weekly sessions of MBRPs. Six months later, a follow-up interview is conducted through telephone to assess cocaine use. This study found that ketamine is associated with lower levels of cocaine use, craving, and time to relapse. A significantly greater proportion of people remained abstinent during the 6-month interview. This study shows the potential of using ketamine as a pharmacotherapy in conjunction with behavioral therapy to treat CUD.[111] However, future studies with larger, more diverse samples and objective evaluations of cocaine use at 6 months are needed to assess the effectiveness of subanesthetic ketamine better.

Although abstinence is often the primary goal in CUD interventions, recent research confirms that reducing cocaine use can be considered a viable treatment outcome for cocaine-dependent individuals.[112] For instance, Amin-Esmaeili *et al.*[113] analyzed data from 13 randomized controlled clinical trials on pharmacological interventions for cocaine or methamphetamine use disorder. They found that individuals who reduced their use frequency from high to low experienced improvements in drug-related symptoms, cravings, and comorbid depression scores. Notably, a significant portion of these individuals tested negative for drugs in urine tests 1 month later, indicating that reduced use can improve quality of life and support further reductions.

Similarly, Roos *et al.*[114] used data from seven randomized controlled trials for CUD to evaluate the clinical utility of reduction in cocaine use frequency as a non-abstinence endpoint. The investigators separated participants into three levels at baseline and end-of-treatment (EOT): Abstinence, low frequency, and high frequency. In general,

individuals who reached the low-frequency level at EOT had similar outcomes as those who reduced to abstinence and significantly better outcomes than those who remained at the high-frequency level. Specifically, at 12-month follow-up, participants with at least one level of reduction at EOT displayed fewer psychological problems, employment issues, and cocaine use days. This study demonstrates that cocaine use reduction can improve overall well-being in the long term. Considering these results, reduced use should become an acceptable treatment objective in CUD interventions.

Supporting this perspective, the Substance Abuse and Mental Health Service administration released an advisory in 2023 encouraging "low barrier care," which emphasizes harm reduction by setting substance use reduction – not abstinence – as a primary goal.[115] This is supported by the U.S. FDA's guidance stating that outcomes other than total abstinence are acceptable endpoints for cocaine addiction clinical trials.[116] While abstinence remains the ideal goal, participants with high use at baseline may deem abstinence as unattainable. The introduction of reduced use as a primary goal could motivate cocaine-dependent individuals to work gradually toward abstinence. Given its potential to reduce cocaine use and the clinical validity of reduction as an outcome, subanesthetic ketamine should be regarded as a promising pharmacological option for CUD.

8. Ketamine versus other pharmacotherapy as CUD harm-reduction strategy

At present, the standard treatment for CUD primarily involves psychosocial treatments, which include cognitive behavioral therapy, motivational interviewing, and group drug counseling.[117] Although there are no current FDA-approved therapeutical treatments for CUD, several medications have been used for their off-label effects on patients who do not respond well to psychosocial therapies.

For instance, topiramate, an anti-seizure medication that activates GABA and decreases dopamine release, is sometimes used at low doses to augment CUD psychosocial treatment.[117,118] Some studies find it more effective than a placebo in reducing weekly cocaine use and suppressing the reinforcing effects of cocaine.[119] However, conflicting clinical trial results indicate that further research is needed to confirm its effectiveness. Another option for patients unresponsive to topiramate is long-acting amphetamines. Although clinical trials did find them effective in reducing cocaine use, most trials reported poor retention rates. In addition, as a DAT inhibitor similar to cocaine, amphetamine's risk of misuse cannot be overlooked.[117]

Another medication, disulfiram, traditionally used to treat alcohol dependence, has shown some efficacy in increasing abstinence rates compared to a placebo. However, it does not significantly affect the frequency or amount of cocaine use compared to placebo, although it does reduce the frequency of cocaine use when compared to naltrexone.[23,120]

Ketamine, however, has several potential advantages for managing CUD. Like all other medications mentioned, ketamine has been shown to reduce cocaine cravings and promote abstinence in multiple clinical trials.[121] In the meantime, its rapid antidepressant effects[120] may help CUD patients cope with withdrawal-related depressive symptoms, aiding in remission. In addition, ketamine targets NMDARs to modulate the DAergic pathway, offering an alternative for individuals unresponsive to other treatments. Therefore, compared to other treatments often associated with barriers such as stigma, addiction risk, and limited accessibility,[119] ketamine's unique properties and rapid action make it a promising alternative for reducing the harm associated with CUD.

9. Conclusion

Subanesthetic ketamine shows promise as a pharmacological intervention for CUD. Growing evidence highlights its ability to reduce cocaine consumption in dependent individuals. Pre-clinical research has demonstrated that a single subanesthetic dose of ketamine can reduce cue-induced craving, suppress drug-seeking behaviors, and increase executive control over reward-based decision-making.[22,19] Furthermore, human subjects exhibited decreased cocaine self-administration, craving, and enhanced motivation to quit cocaine after a single ketamine infusion.[31,24]

Although ketamine reduces cocaine misuse, there is mixed evidence that subanesthetic ketamine leads to long-term abstinence. However, recent findings suggest that a reduction in cocaine consumption is as clinically significant as achieving abstinence.[113,114] Thus, even if sobriety remains the ultimate objective, reduced cocaine use should be considered a valuable measure of improvement in CUD treatment.

Despite ketamine's potential for abuse,[26] its context-dependent nature allows for the safe administration of subanesthetic ketamine to individuals with CUD under the supervision of health-care professionals, similar to the use of Spravato as depression therapy.[19,26,122] Before integrating subanesthetic ketamine as a harm-reduction strategy for CUD into clinical practice, additional research must delineate ketamine's mechanism of action against cocaine. Current research suggests that ketamine may alleviate CUD by modulating the dopaminergic system by altering dopamine levels directly, increasing BDNF

levels, or blocking LHB-bursting neurons. In addition, pre-clinical research shows sex-dependent differences in ketamine response, although the mechanism responsible for this phenomenon is still unclear.

Despite the significant advancement in ketamine research, most studies relied on anti-depressant animal models. To explore ketamine's full potential in treating CUD, more clinical and pre-clinical studies should focus specifically on ketamine's mechanisms and effects using a CUD model. In addition, future investigations should also establish optimal dose and frequency schedules to maximize patient safety and foster durable therapeutic outcomes.[119]

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Conflict of interest

The authors declare they have no competing interests.

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References

1. Roque Bravo R, Faria AC, Brito-da-Costa AM, *et al*. Cocaine: An updated overview on chemistry, detection, biokinetics, and pharmacotoxicological aspects including abuse pattern. *Toxins* (*Basel*). 2022;14(4):278.

   doi: 10.3390/toxins14040278

2. Available from: https://www.unodc.org/documents/data-and-analysis/cocaine/Global_cocaine_report_2023.pdf [Last accessed on 2024 Jul 29].

3. *Stimulant Use Disorder*. *PsychDB*; 2022. Available from: https://www.psychdb.com/addictions/stimulants/1-use-disorder [Last accessed on 2024 Jul 29].

4. Ostlund SB, Halbout B. Mesolimbic dopamine signaling in cocaine addiction. In: Preedy VR, editor. *The Neuroscience of Cocaine*. Ch. 29. United States: Academic Press; 2017. p. 287-295.

   doi: 10.1016/B978-0-12-803750-8.00029-4

5. Bocklisch C, Pascoli V, Wong JCY, *et al*. Cocaine disinhibits dopamine neurons by potentiation of GABA transmission in the ventral tegmental area. *Science*. 2013;341(6153):1521-1525.

   doi: 10.1126/science.1237059

6. Soares-Cunha C, de Vasconcelos NAP, Coimbra B, *et al*. Nucleus accumbens medium spiny neurons subtypes signal both reward and aversion. *Mol Psychiatry*. 2020;25(12):3241-3255.

   doi: 10.1038/s41380-019-0484-3

7. Liu Z, Le Q, Lv Y, *et al*. A distinct D1-MSN subpopulation down-regulates dopamine to promote negative emotional state. *Cell Res*. 2022;32(2):139-156.

   doi: 10.1038/s41422-021-00588-5

8. Gong S, Fayette N, Heinsbroek JA, Ford CP. Cocaine shifts dopamine D2 receptor sensitivity to gate conditioned behaviors. *Neuron*. 2021;109(21):3421-3435.e5.

   doi: 10.1016/j.neuron.2021.08.012

9. Can A, Zanos P, Moaddel R, *et al*. Effects of ketamine and ketamine metabolites on evoked striatal dopamine release, dopamine receptors, and monoamine transporters. *J Pharmacol Exp Ther*. 2016;359(1):159-170.

   doi: 10.1124/jpet.116.235838

10. Wright WJ, Dong Y. Psychostimulant-induced adaptations in nucleus accumbens glutamatergic transmission. *Cold Spring Harb Perspect Med*. 2020;10(12):a039255.

    doi: 10.1101/cshperspect.a039255

11. Calipari ES, Bagot RC, Purushothaman I, *et al*. *In vivo* imaging identifies temporal signature of D1 and D2 medium spiny neurons in cocaine reward. *Proc Natl Acad Sci*. 2016;113(10):2726-2731.

    doi: 10.1073/pnas.1521238113

12. Wright WJ, Graziane NM, Neumann PA, *et al*. Silent synapses dictate cocaine memory destabilization and reconsolidation. *Nat Neurosci*. 2020;23(1):32-46.

    doi: 10.1038/s41593-019-0537-6

13. Chiamulera C, Piva A, Abraham WC. Glutamate receptors and metaplasticity in addiction. *Curr Opin Pharmacol*. 2021;56:39-45.

    doi: 10.1016/j.coph.2020.09.005

14. Cepeda C, André VM, Jocoy EL, Levine MS. NMDA and dopamine: Diverse mechanisms applied to interacting

receptor systems. In: Van Dongen AM, editor. *Biology of the NMDA Receptor*. *Frontiers in Neuroscience*. CRC Press/Taylor & Francis; 2009. Available from: https://www.ncbi.nlm.nih.gov/books/NBK5280 [Last accessed on 2024 Jul 30].

15. Wang YQ, Huang YH, Balakrishnan S, *et al*. AMPA and NMDA receptor trafficking at cocaine-generated synapses. *J Neurosci*. 2021;41(9):1996-2011.

    doi: 10.1523/JNEUROSCI.1918-20.2021

16. Gautam CS, Mahajan SS, Sharma J, Singh H, Singh J. Repurposing potential of ketamine: Opportunities and challenges. *Indian J Psychol Med*. 2020;42(1):22-29.

    doi: 10.4103/IJPSYM.IJPSYM_228_19

17. *Club Drugs*. Available from: https://www.nyc.gov/site/doh/health/health-topics/club-drugs.page [Last accessed on 2024 Jul 31].

18. Chaves TV, Wilffert B, Sanchez ZM. Overdoses and deaths related to the use of ketamine and its analogues: A systematic review. *Am J Drug Alcohol Abuse*. 2023;49(2):141-150.

    doi: 10.1080/00952990.2022.2132506

19. Maltbie EA, Gopinath KS, Howell LL. Effects of ketamine treatment on cocaine-induced reinstatement and disruption of functional connectivity in unanesthetized rhesus monkeys. *Psychopharmacology* (*Berl*). 2019;236(7):2105-2118.

    doi: 10.1007/s00213-019-05204-4

20. Xu L, Nan J, Lan Y. The nucleus accumbens: A common target in the comorbidity of depression and addiction. *Front Neural Circuits*. 2020;14:37.

    doi: 10.3389/fncir.2020.00037

21. Sinha R. The clinical neurobiology of drug craving. *Curr Opin Neurobiol*. 2013;23(4):649-654.

    doi: 10.1016/j.conb.2013.05.001

22. Fitzpatrick CJ, Morrow JD. Subanesthetic ketamine decreases the incentive-motivational value of reward-related cues. *J Psychopharmacol Oxf Engl*. 2017;31(1):67-74.

    doi: 10.1177/0269881116667709

23. Gao Z, Winhusen TJ, Gorenflo M, *et al*. Repurposing ketamine to treat cocaine use disorder: Integration of artificial intelligence-based prediction, expert evaluation, clinical corroboration and mechanism of action analyses. *Addiction*. 2023;118(7):1307-1319.

    doi: 10.1111/add.16168

24. Dakwar E, Levin F, Foltin RW, Nunes EV, Hart CL. The effects of subanesthetic ketamine infusions on motivation to quit and cue-induced craving in cocaine-dependent research volunteers. *Biol Psychiatry*. 2014;76(1):40-46.

    doi: 10.1016/j.biopsych.2013.08.009

25. Dakwar E, Hart CL, Levin FR, Nunes EV, Foltin RW. Cocaine self-administration disrupted by the N-methyl-D-aspartate receptor antagonist ketamine: A randomized, crossover trial. *Mol Psychiatry*. 2017;22(1):76-81.

    doi: 10.1038/mp.2016.39

26. Le TT, Cordero IP, Jawad MY, *et al*. The abuse liability of ketamine: A scoping review of preclinical and clinical studies. *J Psychiatr Res*. 2022;151:476-496.

    doi: 10.1016/j.jpsychires.2022.04.035

27. Palamar JJ, Fitzgerald ND, Grundy DJ, Black JC, Jewell JS, Cottler LB. Characteristics of poisonings involving ketamine in the United States, 2019–2021. *J Psychopharmacol* (*Oxf*). 2023;37(8):802-808.

    doi: 10.1177/02698811221140006

28. Simmler LD, Li Y, Hadjas LC, Hiver A, van Zessen R, Lüscher C. Dual action of ketamine confines addiction liability. *Nature*. 2022;608(7922):368-373.

    doi: 10.1038/s41586-022-04993-7

29. Schoepfer KJ, Strong CE, Saland SK, Wright KN, Kabbaj M. Sex-and dose-dependent abuse liability of repeated subanesthetic ketamine in rats. *Physiol Behav*. 2019;203:60-69.

    doi: 10.1016/j.physbeh.2017.10.021

30. Bonaventura J, Lam S, Carlton M, *et al*. Pharmacological and behavioral divergence of ketamine enantiomers: Implications for abuse liability. *Mol Psychiatry*. 2021;26(11):6704-6722.

    doi: 10.1038/s41380-021-01093-2

31. Elersič K, Banjac A, Živin M, Zorović M. Behavioral sensitization and tolerance induced by repeated treatment with ketamine enantiomers in male Wistar rats. *PLoS One*. 2024;19(3):e0299379.

    doi: 10.1371/journal.pone.0299379

32. *Commissioner O of the*. *FDA Approves New Nasal Spray Medication for Treatment-Resistant Depression; Available Only at a Certified Doctor's Office or Clinic*. FDA; 2020. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified [Last accessed on 2024 Jul 30.

33. *Ketamine for Intractable Headache*. *Practical Neurology*. Available from: https://practicalneurology.com/articles/2022-nov-dec/ketamine-for-intractable-headache [Last accessed on 2024 Jun 29.

34. Rothberg RL, Azhari N, Haug NA, Dakwar E. Mystical-type experiences occasioned by ketamine mediate its impact on at-risk drinking: Results from a randomized, controlled trial. *J Psychopharmacol* (*Oxf*). 2021;35(2):150-158.

    doi: 10.1177/0269881120970879

35. Dakwar E, Anerella C, Hart CL, Levin FR, Mathew SJ, Nunes EV. Therapeutic infusions of ketamine: Do the psychoactive effects matter? *Drug Alcohol Depend*. 2014;136:153-157.

doi: 10.1016/j.drugalcdep.2013.12.019

36. Dakwar E, Nunes E, Hart C, Hu M, Foltin R, Levin F. A sub-set of psychoactive effects may be critical to the behavioral impact of ketamine on cocaine use disorder: Results from a randomized, controlled laboratory study. *Neuropharmacology*. 2018;142:270-276.

doi: 10.1016/j.neuropharm.2018.01.005

37. Chan B, Kondo K, Freeman M, Ayers C, Montgomery J, Kansagara D. Pharmacotherapy for cocaine use disorder-a systematic review and meta-analysis. *J Gen Intern Med*. 2019;34(12):2858-2873.

doi: 10.1007/s11606-019-05074-8

38. Angarita GA, Hadizadeh H, Cerdena I, Potenza MN. Can pharmacotherapy improve treatment outcomes in people with co-occurring major depressive and cocaine use disorders? *Expert Opin Pharmacother*. 2021;22(13):1669-1683.

doi: 10.1080/14656566.2021.1931684

39. Carey TL. Use of antidepressants in patients with co-occurring depression and substance use disorders. In: Macaluso M, Preskorn SH, editors. *Antidepressants: From Biogenic Amines to New Mechanisms of Action*. Berlin: Springer International Publishing; 2019. p. 359-370.

doi: 10.1007/164_2018_162

40. Aharonovich E, Scodes J, Wall MM, Hasin DS. The relationship of frequency of cocaine use to substance and psychiatric disorders in the U.S. general population. *Drug Alcohol Depend*. 2021;227:108933.

doi: 10.1016/j.drugalcdep.2021.108933

41. Samet S, Fenton MC, Nunes E, Greenstein E, Aharonovich E, Hasin D. Effects of independent and substance-induced major depressive disorder on remission and relapse of alcohol, cocaine and heroin dependence. *Addiction*. 2013;108(1):115-123.

doi: 10.1111/j.1360-0443.2012.04010.x

42. Zilkha N, Barnea-Ygael N, Keidar L, Zangen A. Increased relapse to cocaine-seeking in a genetic model for depression. *Addict Biol*. 2020;25(3):e12756.

doi: 10.1111/adb.12756

43. Cabé J, Brousse G, Pereira B, *et al*. Influence of clinical markers of dopaminergic behaviors on depressive symptoms during withdrawal in cocaine users. *Front Psychiatry*. 2021;12:775670.

doi: 10.3389/fpsyt.2021.775670

44. Tobón KE, Catuzzi JE, Cote SR, Sonaike A, Kuzhikandathil EV. Post-transcriptional regulation of dopamine D1 receptor expression in caudate-putamen of cocaine-sensitized mice. *Eur J Neurosci*. 2015;42(2):1849-1857.

doi: 10.1111/ejn.12933

45. Park K, Volkow ND, Pan Y, Du C. Chronic cocaine dampens dopamine signaling during cocaine intoxication and unbalances D1 over D2 receptor signaling. *J Neurosci*. 2013;33(40):15827-15836.

doi: 10.1523/JNEUROSCI.1935-13.2013

46. Kaushik S, Ahmad F, Choudhary S, *et al*. Critical appraisal and systematic review of genes linked with cocaine addiction, depression and anxiety. *Neurosci Biobehav Rev*. 2023;152:105270.

doi: 10.1016/j.neubiorev.2023.105270

47. Dackis CA, Gold MS. New concepts in cocaine addiction: The dopamine depletion hypothesis. *Neurosci Biobehav Rev*. 1985;9(3):469-477.

doi: 10.1016/0149-7634(85)90022-3

48. Volkow ND, Tomasi D, Wang GJ, *et al*. Stimulant-induced dopamine increases are markedly blunted in active cocaine abusers. *Mol Psychiatry*. 2014;19(9):1037-1043.

doi: 10.1038/mp.2014.58

49. Cui L, Li S, Wang S, *et al*. Major depressive disorder: Hypothesis, mechanism, prevention and treatment. *Signal Transduct Target Ther*. 2024;9(1):1-32.

doi: 10.1038/s41392-024-01738-y

50. Deng J, Zhang T, Zheng X, Shang L, Zhan CG, Zheng F. Recovery of dopaminergic system after cocaine exposure and impact of a long-acting cocaine hydrolase. *Addict Biol*. 2022;27(4):e13179.

doi: 10.1111/adb.13179

51. Belujon P, Grace AA. Restoring mood balance in depression: Ketamine reverses deficit in dopamine-dependent synaptic plasticity. *Biol Psychiatry*. 2014;76(12):927-936.

doi: 10.1016/j.biopsych.2014.04.014

52. Witkin JM, Monn JA, Schoepp DD, *et al*. The rapidly acting antidepressant ketamine and the mGlu2/3 receptor antagonist LY341495 rapidly engage dopaminergic mood circuits. *J Pharmacol Exp Ther*. 2016;358(1):71-82.

doi: 10.1124/jpet.116.233627

53. Li Y, Zhu ZR, Ou BC, *et al*. Dopamine D2/D3 but not dopamine D1 receptors are involved in the rapid antidepressant-like effects of ketamine in the forced swim test. *Behav Brain Res*. 2015;279:100-105.

doi: 10.1016/j.bbr.2014.11.016

54. Li X jin, Yu J han, Wu X, *et al*. Ketamine enhances dopamine D1 receptor expression by modulating microRNAs in a ketamine-induced schizophrenia-like mouse model. *Neurotoxicol Teratol*. 2022;91:107079.

doi: 10.1016/j.ntt.2022.107079

55. Hare BD, Shinohara R, Liu RJ, Pothula S, DiLeone RJ, Duman RS. Optogenetic stimulation of medial prefrontal

cortex Drd1 neurons produces rapid and long-lasting antidepressant effects. *Nat Commun*. 2019;10(1):223.

doi: 10.1038/s41467-018-08168-9

56. Galvanho JP, Manhães AC, Carvalho-Nogueira ACC, Silva JM, Filgueiras CC, Abreu-Villaça Y. Profiling of behavioral effects evoked by ketamine and the role of 5HT2 and D2 receptors in ketamine-induced locomotor sensitization in mice. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020;97:109775.

doi: 10.1016/j.pnpbp.2019.109775

57. Bock R, Shin JH, Kaplan AR, *et al*. Strengthening the accumbal indirect pathway promotes resilience to compulsive cocaine use. *Nat Neurosci*. 2013;16(5):632-638.

doi: 10.1038/nn.3369

58. Hanada T. Ionotropic glutamate receptors in epilepsy: A review focusing on AMPA and NMDA receptors. *Biomolecules*. 2020;10(3):464.

doi: 10.3390/biom10030464

59. Cavalleri L, Merlo Pich E, Millan MJ, *et al*. Ketamine enhances structural plasticity in mouse mesencephalic and human iPSC-derived dopaminergic neurons via AMPAR-driven BDNF and mTOR signaling. *Mol Psychiatry*. 2018;23(4):812-823.

doi: 10.1038/mp.2017.241

60. El Iskandrani KS, Oosterhof CA, El Mansari M, Blier P. Impact of subanesthetic doses of ketamine on AMPA-mediated responses in rats: An *in vivo* electrophysiological study on monoaminergic and glutamatergic neurons. *J Psychopharmacol* (*Oxf*). 2015;29(7):792-801.

doi: 10.1177/0269881115573809

61. Liu Y, Lin D, Wu B, Zhou W. Ketamine abuse potential and use disorder. *Brain Res Bull*. 2016;126:68-73.

doi: 10.1016/j.brainresbull.2016.05.016

62. Sun Z, Ma Y, Xie L, *et al*. Behavioral changes and neuronal damage in rhesus monkeys after 10 weeks of ketamine administration involve prefrontal cortex dopamine D2 receptor and dopamine transporter. *Neuroscience*. 2019;415:97-106.

doi: 10.1016/j.neuroscience.2019.07.022

63. Wu M, Minkowicz S, Dumrongprechachan V, Hamilton P, Kozorovitskiy Y. Ketamine rapidly enhances glutamate-evoked dendritic spinogenesis in medial prefrontal cortex through dopaminergic mechanisms. *Biol Psychiatry*. 2021;89(11):1096-1105.

doi: 10.1016/j.biopsych.2020.12.022

64. Abdel-Hay N, Kabirova M, Yaka R. A discrete subpopulation of PFC-LHb neurons govern cocaine place preference. *Transl Psychiatry*. 2024;14(1):1-11.

doi: 10.1038/s41398-024-02988-8

65. Weiss T, Veh RW. Morphological and electrophysiological characteristics of neurons within identified subnuclei of the lateral habenula in rat brain slices. *Neuroscience*. 2011;172:74-93.

doi: 10.1016/j.neuroscience.2010.10.047

66. Yang Y, Cui Y, Sang K, *et al*. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. *Nature*. 2018;554(7692):317-322.

doi: 10.1038/nature25509

67. Cui Y, Yang Y, Ni Z, *et al*. Astroglial Kir4.1 in the lateral habenula drives neuronal bursts in depression. *Nature*. 2018;554(7692):323-327.

doi: 10.1038/nature25752

68. Cui Y, Hu S, Hu H. Lateral habenular burst firing as a target of the rapid antidepressant effects of ketamine. *Trends Neurosci*. 2019;42(3):179-191.

doi: 10.1016/j.tins.2018.12.002

69. Ma S, Chen M, Jiang Y, *et al*. Sustained antidepressant effect of ketamine through NMDAR trapping in the LHb. *Nature*. 2023;622(7984):802-809.

doi: 10.1038/s41586-023-06624-1

70. Meye FJ, Valentinova K, Lecca S, *et al*. Cocaine-evoked negative symptoms require AMPA receptor trafficking in the lateral habenula. *Nat Neurosci*. 2015;18(3):376-378.

doi: 10.1038/nn.3923

71. Diering GH, Heo S, Hussain NK, Liu B, Huganir RL. Extensive phosphorylation of AMPA receptors in neurons. *Proc Natl Acad Sci*. 2016;113(33):E4920-E4927.

doi: 10.1073/pnas.1610631113

72. Li X, Wolf ME. Multiple faces of BDNF in cocaine addiction. *Behav Brain Res*. 2015;279:240-254.

doi: 10.1016/j.bbr.2014.11.018

73. Brunoni AR, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: Implications for the role of neuroplasticity in depression. *Int J Neuropsychopharmacol*. 2008;11(8):1169-1180.

doi: 10.1017/S1461145708009309

74. Miuli A, d'Andrea G, Pettorruso M, *et al*. From a cycle to a period: The potential role of BDNF as plasticity and phase-specific biomarker in cocaine use disorder. *Curr Neuropharmacol*. 2022;20(11):2024-2028.

doi: 10.2174/1570159X20666220114152052

75. Pianca TG, Rosa RL, Ceresér KMM, *et al*. Differences in biomarkers of crack-cocaine adolescent users before/after abstinence. *Drug Alcohol Depend*. 2017;177:207-213.

doi: 10.1016/j.drugalcdep.2017.03.043

76. von Diemen L, Kapczinski F, Sordi AO, *et al*. Increase in brain-derived neurotrophic factor expression in early crack cocaine withdrawal. *Int J Neuropsychopharmacol*. 2014;17(1):33-40.

doi: 10.1017/S146114571300103X

77. Corominas-Roso M, Roncero C, Eiroa-Orosa FJ, *et al*. Brain-derived neurotrophic factor serum levels in cocaine-dependent patients during early abstinence. *Eur Neuropsychopharmacol*. 2013;23(9):1078-1084.

doi: 10.1016/j.euroneuro.2012.08.016

78. Le Foll B, Diaz J, Sokoloff P. A single cocaine exposure increases BDNF and D3 receptor expression: Implications for drug-conditioning. *Neuroreport*. 2005;16(2):175.

doi: 10.1097/00001756-200502080-00022

79. Ornell F, Hansen F, Schuch FB, *et al*. Brain-derived neurotrophic factor in substance use disorders: A systematic review and meta-analysis. *Drug Alcohol Depend*. 2018;193:91-103.

doi: 10.1016/j.drugalcdep.2018.08.036

80. Cavaleri D, Moretti F, Bartoccetti A, *et al*. The role of BDNF in major depressive disorder, related clinical features, and antidepressant treatment: Insight from meta-analyses. *Neurosci Biobehav Rev*. 2023;149:105159.

doi: 10.1016/j.neubiorev.2023.105159

81. Pettorruso M, Miuli A, Clemente K, *et al*. Enhanced peripheral levels of BDNF and proBDNF: Elucidating neurotrophin dynamics in cocaine use disorder. *Mol Psychiatry*. 2024;29(3):760-766.

doi: 10.1038/s41380-023-02367-7

82. Fonseca F, Mestre-Pinto JI, Rodríguez-Minguela R, *et al*. BDNF and cortisol in the diagnosis of cocaine-induced depression. *Front Psychiatry*. 2022;13:836771.

doi: 10.3389/fpsyt.2022.836771

83. Tooley J, Marconi L, Alipio J, *et al*. Glutamatergic ventral pallidal neurons modulate activity of the habenula-tegmental circuitry and constrain reward seeking. *Biol Psychiatry*. 2018;83(12):1012-1023.

doi: 10.1016/j.biopsych.2018.01.003

84. Viana GSB, Vale EM, Araujo ARA, *et al*. Rapid and long-lasting antidepressant-like effects of ketamine and their relationship with the expression of brain enzymes, BDNF, and astrocytes. *Braz J Med Biol Res*. 2020;54:e10107.

doi: 10.1590/1414-431X202010107

85. Zheng W, Zhou YL, Wang CY, *et al*. Plasma BDNF concentrations and the antidepressant effects of six ketamine infusions in unipolar and bipolar depression. *PeerJ*. 2021;9:e10989.

doi: 10.7717/peerj.10989

86. Woelfer M, Li M, Colic L, *et al*. Ketamine-induced changes in plasma brain-derived neurotrophic factor (BDNF) levels are associated with the resting-state functional connectivity of the prefrontal cortex. *World J Biol Psychiatry*. 2020;21(9):696-710.

doi: 10.1080/15622975.2019.1679391

87. Haile CN, Murrough JW, Iosifescu DV, *et al*. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. *Int J Neuropsychopharmacol*. 2014;17(2):331-336.

doi: 10.1017/S1461145713001119

88. Berglind WJ, Whitfield TW, LaLumiere RT, Kalivas PW, McGinty JF. A single intra-PFC infusion of BDNF prevents cocaine-induced alterations in extracellular glutamate within the nucleus accumbens. *J Neurosci*. 2009;29(12):3715-3719.

doi: 10.1523/JNEUROSCI.5457-08.2009

89. Schmidt HD, Sangrey GR, Darnell SB, *et al*. Increased brain-derived neurotrophic factor (BDNF) expression in the ventral tegmental area during cocaine abstinence is associated with increased histone acetylation at BDNF exon I-containing promoters. *J Neurochem*. 2012;120(2):202-209.

doi: 10.1111/j.1471-4159.2011.07571.x

90. McGinty JF, Whitfield TW, Berglind WJ. Brain-derived neurotrophic factor and cocaine addiction. *Brain Res*. 2010;1314:183-193.

doi: 10.1016/j.brainres.2009.08.078

91. Sarkar A, Kabbaj M. Sex differences in effects of ketamine on behavior, spine density, and synaptic proteins in socially isolated rats. *Biol Psychiatry*. 2016;80(6):448-456.

doi: 10.1016/j.biopsych.2015.12.025

92. Thelen C, Sens J, Mauch J, Pandit R, Pitychoutis PM. Repeated ketamine treatment induces sex-specific behavioral and neurochemical effects in mice. *Behav Brain Res*. 2016;312:305-312.

doi: 10.1016/j.bbr.2016.06.041

93. Ponton E, Turecki G, Nagy C. Sex differences in the behavioral, molecular, and structural effects of ketamine treatment in depression. *Int J Neuropsychopharmacol*. 2022;25(1):75-84.

doi: 10.1093/ijnp/pyab082

94. Saland SK, Schoepfer KJ, Kabbaj M. Hedonic sensitivity to low-dose ketamine is modulated by gonadal hormones in a sex-dependent manner. *Sci Rep*. 2016;6(1):21322.

doi: 10.1038/srep21322

95. Ardalan M, Elfving B, Rafati AH, *et al*. Rapid effects of S-ketamine on the morphology of hippocampal astrocytes and BDNF serum levels in a sex-dependent manner. *Eur Neuropsychopharmacol*. 2020;32:94-103.

doi: 10.1016/j.euroneuro.2020.01.001

96. Dossat AM, Wright KN, Strong CE, Kabbaj M. Behavioral and biochemical sensitivity to low doses of ketamine: Influence of estrous cycle in C57BL/6 mice. *Neuropharmacology*. 2018;130:30-41.

doi: 10.1016/j.neuropharm.2017.11.022

97. Highland JN, Farmer CA, Zanos P, *et al*. Sex-dependent metabolism of ketamine and (2R,6R)-hydroxynorketamine in mice and humans. *J Psychopharmacol* (*Oxf*). 2022;36(2):170-182.

doi: 10.1177/02698811211064922

98. Di Ianni T, Ewbank SN, Levinstein MR, *et al*. Sex dependence of opioid-mediated responses to subanesthetic ketamine in rats. *Nat Commun*. 2024;15(1):893.

doi: 10.1038/s41467-024-45157-7

99. Klein ME, Chandra J, Sheriff S, Malinow R. Opioid system is necessary but not sufficient for antidepressive actions of ketamine in rodents. *Proc Natl Acad Sci U S A*. 2020;117(5):2656-2662.

doi: 10.1073/pnas.1916570117

100. Marton T, Barnes DE, Wallace A, Woolley JD. Concurrent use of buprenorphine, methadone, or naltrexone does not inhibit ketamine's antidepressant activity. *Biol Psychiatry*. 2019;85(12):e75-e76.

doi: 10.1016/j.biopsych.2019.02.008

101. Strong CE, Schoepfer KJ, Dossat AM, Saland SK, Wright KN, Kabbaj M. Locomotor sensitization to intermittent ketamine administration is associated with nucleus accumbens plasticity in male and female rats. *Neuropharmacology*. 2017;121:195-203.

doi: 10.1016/j.neuropharm.2017.05.003

102. Liu CL, Wang YK, Jin GZ, Shi WX, Gao M. Cocaine-induced locomotor sensitization associates with slow oscillatory firing of neurons in the ventral tegmental area. *Sci Rep*. 2018;8(1):3274.

doi: 10.1038/s41598-018-21592-7

103. Valjent E, Bertran-Gonzalez J, Aubier B, Greengard P, Hervé D, Girault JA. Mechanisms of locomotor sensitization to drugs of abuse in a two-injection protocol. *Neuropsychopharmacology*. 2010;35(2):401-415.

doi: 10.1038/npp.2009.143

104. Garcia-Carachure I, Flores-Ramirez FJ, Castillo SA, *et al*. Enduring effects of adolescent ketamine exposure on cocaine- and sucrose-induced reward in male and female C57BL/6 mice. *Neuropsychopharmacology*. 2020;45(9):1536-1544.

doi: 10.1038/s41386-020-0654-7

105. McDougall SA, Park GI, Ramirez GI, Gomez V, Adame BC, Crawford CA. Sex-dependent changes in ketamine-induced locomotor activity and ketamine pharmacokinetics in preweanling, adolescent, and adult rats. *Eur Neuropsychopharmacol*. 2019;29(6):740-755.

doi: 10.1016/j.euroneuro.2019.03.013

106. Chen WC, Wang TS, Chang FY, Chen PA, Chen YC. Age, dose, and locomotion: Decoding vulnerability to ketamine in C57BL/6J and BALB/c mice. *Biomedicines*. 2023;11(7):1821.

doi: 10.3390/biomedicines11071821

107. Nicolas C, Russell TI, Pierce AF, *et al*. Incubation of cocaine craving after intermittent-access self-administration: Sex differences and estrous cycle. *Biol Psychiatry*. 2019;85(11):915-924.

doi: 10.1016/j.biopsych.2019.01.015

108. Kokane SS, Perrotti LI. Sex differences and the role of estradiol in mesolimbic reward circuits and vulnerability to cocaine and opiate addiction. *Front Behav Neurosci*. 2020;14:74.

doi: 10.3389/fnbeh.2020.00074

109. Freeman MP, Papakostas GI, Hoeppner B, *et al*. Sex differences in response to ketamine as a rapidly acting intervention for treatment resistant depression. *J Psychiatr Res*. 2019;110:166-171.

doi: 10.1016/j.jpsychires.2019.01.010

110. Benitah K, Siegel AN, Lipsitz O, *et al*. Sex differences in ketamine's therapeutic effects for mood disorders: A systematic review. *Psychiatry Res*. 2022;312:114579.

doi: 10.1016/j.psychres.2022.114579

111. Dakwar E, Nunes EV, Hart CL, *et al*. A single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: A randomized clinical trial. *Am J Psychiatry*. 2019;176(11):923-930.

doi: 10.1176/appi.ajp.2019.18101123

112. *Abuse NI on D. Reduced Drug Use is a Meaningful Treatment Outcome for People with Stimulant Use Disorders*. National Institute on Drug Abuse (NIDA); 2024. Available from: https://nida.nih.gov/news-events/news-releases/2024/01/reduced-drug-use-is-a-meaningful-treatment-outcome-for-people-with-stimulant-use-disorders [Last accessed on 2024 Jul 30].

113. Amin-Esmaeili M, Farokhnia M, Susukida R, *et al*. Reduced drug use as an alternative valid outcome in individuals with stimulant use disorders: Findings from 13 multisite randomized clinical trials. *Addict Abingdon Engl*. 2024;119(5):833-843.

doi: 10.1111/add.16409

114. Roos CR, Nich C, Mun CJ, *et al*. Clinical validation of reduction in cocaine frequency level as an endpoint in clinical trials for cocaine use disorder. *Drug Alcohol Depend*. 2019;205:107648.

doi: 10.1016/j.drugalcdep.2019.107648

115. *Low Barrier Models of Care for Substance Use Disorders. Samhsa.gov*; 2024. Available from: www.samhsa.gov/resource/spark/low-barrier-models-care-substance-use-disorders [Last accessed on 2024 Dec 26].

116. Facher L. *Drug Treatment that Insists on Abstinence? Federal Agencies are Just Saying no. STAT*; 2024. Available from: https://www.statnews.com/2024/05/31/drug-policy-shifts-from-abstinence-to-harm-reduction [Last accessed on 2024 Jul 30].

117. Kampman K. *Stimulant Use Disorder: Treatment Overview. UpToDate*. Available from: https://www.uptodate.com/contents/stimulant-use-disorder-treatment-overview?search=cocaine%20use%20disorder&topicRef=7802&source=see_link#H1717002511 [Last accessed on 2024 Nov 15].

118. *Topiramate: Drug Information. UpToDate*. Available from: https://www.uptodate.com/contents/topiramate-drug-information?search=cocaine+use+disorder&topicRef=106878&source=see_link#F229242 [Last accessed on 2024 Nov 15].

119. Bentzley BS, Han SS, Neuner S, Humphreys K, Kampman KM, Halpern CH. Comparison of treatments for cocaine use disorder among adults: A systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(5):e218049.

doi: 10.1001/jamanetworkopen.2021.8049

120. Walsh Z, Mollaahmetoglu OM, Rootman J, *et al*. Ketamine for the treatment of mental health and substance use disorders: Comprehensive systematic review. *BJPsych Open*. 2021;8(1):e19.

doi: 10.1192/bjo.2021.1061

121. Slomski A. Ketamine to help treat cocaine use disorder. *JAMA*. 2019;322(8):717.

doi: 10.1001/jama.2019.12352

122. Xin J, Shan W, Li J, Yu H, Zuo Z. Activation of the lateral habenula-ventral tegmental area neural circuit contributes to postoperative cognitive dysfunction in mice. *Adv Sci*. 2022;9(22):2202228.

doi: 10.1002/advs.202202228

123. Lüscher C, Malenka RC. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harb Perspect Biol*. 2012;4(6):a005710.

doi: 10.1101/cshperspect.a005710