International Journal of Community Medicine and Public Health
Albanna AK et al. Int J Community Med Public Health. 2025 Aug;12(8):3793-3799
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20252181

Review Article

Neurological effects of ketamine: mechanisms, addiction potential, and toxicity profiles with focus on Saudi Arabia

Alanoud K. Albanna[1]*, Zayed M. Alnefaie[2], Atheer M. Saleh[1], Fatimah H. Alsayedeash[1], Layan S. Almejmaj[1], Afnan I. Alturki[1], Rawan K. Alnwagha[1], Fay N. Abu Deraa[1], Narjes Al Sabaa[3], Ahmed A. Obaid[4], Mazen Alayidh[5]

[1]Department of Anaesthesiology, Al-Rayan Colleges, Al-Madinah Al-Munawwara, Saudi Arabia
[2]Department of Anatomy and Embryology, Al-Rayan Colleges, Al-Madinah Al-Munawwara, Saudi Arabia
[3]Department of Medicine, Al Rayan Colleges, Al Madinah Al Munawwara, Saudi Arabia
[4]Department of Anesthesia Technology, College of Applied Medical Sciences, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia
[5]College of medicine, King Khalid University, Abha, Saudi Arabia

Received: 07 June 2025
Revised: 11 July 2025
Accepted: 14 July 2025

***Correspondence:**
Dr. Alanoud K. Albanna,
E-mail: Zayedalnefaie@gmail.com

ABSTRACT

Ketamine's rapid action and diverse physiological effects have made it an important drug in both anesthesia and mental health treatment. Clinically, it offers unique dissociative anesthetic properties, preserving stable vital signs during sedation and analgesia. Beyond its numbing effect, studies explore its influence on N-methyl-D-aspartate (NMDA) receptors and wider neurochemical systems linked to its antidepressant action, especially for treatment-resistant depression. While beneficial therapeutically, ketamine's potential for abuse, especially recreationally, is a concern. Brain imaging reveals structural degeneration in brain areas related to memory, emotion, and motor control, due to chronic misuse, resulting in severe neurological changes. Yet, in controlled settings, ketamine displays potential for addiction treatment, as studies reveal decreased cravings and higher abstinence rates, Toxicity is a worry, particularly when ketamine is taken in large quantities or without medical guidance. Potential effects range from hallucinations and heart problems to difficulties with urination and liver damage. Cognitive impairment and psychiatric symptoms are also seen with prolonged use. While generally safe when used as directed, continued research emphasizes the need for strict clinical supervision and further investigation of its long-term consequences.

Keywords: Ketamine, NMDA receptor, Dissociative anesthesia, Antidepressant, Addiction, Neurotoxicity, Brain atrophy

INTRODUCTION

Ketamine, a multifaceted drug, is increasingly important in both anesthesia and psychiatry. Ketamine's introduction to clinical practice began in the 1970s, driven by its versatility, affordability, and distinct pharmacological properties. The combination of wide therapeutic use, a strong safety profile, and convenient storage means it's become essential in surgery and emergency care, particularly when resources such as electricity, oxygen, or advanced monitoring are scarce. As an anesthetic, ketamine is unique because it provides analgesia, hypnosis, and amnesia. It causes a dissociative anesthesia, an electrophysiological disconnection of the limbic system and cortex, permitting surgery with maintained airway reflexes and stable cardiovascular parameters.[1]

Clinical investigations demonstrating ketamine's rapid and effective effects have spurred increased interest in its mechanism of action. By antagonizing N-methyl-D-aspartate (NMDA) receptors non-competitively, ketamine interacts with multiple neural receptors to exert its pharmacological actions. Synaptic plasticity and excitatory neurotransmission depend on this receptor, which is widespread in the central nervous system. Clinical formulations usually comprise a racemic combination of both S(+) and R(–) isomers. Although the R(–) form of ketamine is attractive for antidepressant use because of its longer action and improved side effect profile, its S(+) isomer demonstrates four times greater NMDA receptor affinity and anesthetic potency.[1,2]

While famous for its narcotic and dissociative effects, it can also be addictive. Its potential to distort perception and create euphoric states like a trance makes it prone to recreational misuse. In East and Southeast Asia, where ketamine has been widely used for decades, the growing use of the drug is particularly noticeable. Awareness of ketamine's function in addiction requires an awareness of its strong effects on the prefrontal cortex, hippocampus, and mesolimbic pathway—regions of the brain essential to memory, reward, and decision-making.[3]

However, new research indicates that ketamine may have therapeutic potential for the treatment of addiction itself. Ketamine has been shown in preclinical and clinical studies to be useful in lowering problematic substance usage, including alcohol, heroin, and cocaine. It's important to note that ketamine has been demonstrated to lessen cravings and the frequency of addictive substance self-administration. After a year, detoxified alcoholics treated with ketamine reported much greater rates of abstinence than those undergoing traditional treatment, according to an important study.[4]

The possibility of ketamine abuse persists despite these encouraging findings. If not properly controlled, ketamine's same qualities that enable it to relieve depressive symptoms and repair broken reward systems can also result in psychological dependence. As a result, even though ketamine is a potent new treatment for addiction, it needs to be used in clinical settings that are regulated and structured to reduce the danger of abuse and enhance results.[3,4]

Despite its well-known clinical uses, improper use can result in a variety of harmful side effects. Depending on the dosage and method of administration, acute cases might cause hallucinations, changed mental status, hypertension, and even respiratory depression. Coma, seizures, and rhabdomyolysis have been seen in more severe cases, particularly when ketamine is used with other drugs. Recreational usage raises the risk of toxicity since adulteration and erratic dosages make the clinical picture even more complex. Supportive treatments like sedation, airway protection, and monitoring for neurological or cardiac issues are frequently part of emergency care.[5] Cardiovascular symptoms have been seen in emergency settings, despite the fact that they are typically temporary.[6]

MECHANISM

Due to its impressive and quick antidepressant effects, especially in treatment-resistant depression, ketamine, which was first introduced in the 1960s as a safer substitute for phencyclidine, has made a comeback in recent years. Although ketamine was first used as an anesthetic, its distinct psychotropic qualities and effectiveness in treating severe depression episodes have made it a crucial subject for current neuropharmacological studies. The racemic molecule, which is made up of equal amounts of (R)- and (S)-ketamine, has unique pharmacological and therapeutic characteristics that have created novel treatment options for mood disorders.[7]

Mechanisms of action: beyond NMDA antagonism

Although ketamine is known as a non-competitive NMDA receptor antagonist, there's mounting evidence suggesting other mechanisms contribute to its antidepressant properties. Ketamine's therapeutic efficacy hasn't been reproduced with other NMDAR antagonists, implying more complex or concurrent pathways are at play.[2,8]

NMDA receptor inhibition and disinhibition hypothesis

Ketamine preferentially inhibits NMDARs on GABAergic interneurons, especially those expressing the GluN2D subunit. In areas such as the medial prefrontal cortex, this selective inhibition decreases inhibitory tone on pyramidal neurons, which causes cortical inhibition and increases glutamate. It is thought that these glutamate spikes initiate a series of neural processes that are essential for the drug's rapid antidepressant action.

AMPA receptor activation

One of the most important downstream consequences of elevated glutamate is the activation of AMPA receptors (AMPARs). Preclinical research has confirmed the critical role of AMPARs. It has been shown that inhibition of AMPARs prevents the antidepressant effects of ketamine. This activation appears necessary to initiate downstream pathways, such as the mTORC1 and BDNF-TrkB pathways, that support synaptic plasticity (Figure 1).

The mTORC1 pathway and synaptogenesis

mTORC1 (mammalian target of rapamycin complex 1) is essential for the control of neurogenesis, synaptic plasticity, and protein synthesis. In the prefrontal cortex, ketamine induces mTORC1 signaling, which rapidly increases synaptic protein production and spine density. The long-lasting antidepressant effects seen after a single dose are thought to be caused by these changes. But there are clear isotype differences. The (S)-ketamine antagonist appears to work through mTORC1-dependent

mechanisms, whereas (R)-ketamine may be more dependent on other pathways, such as ERK signalling.[8]

ERK signaling and the (R)-ketamine pathway

Despite having a lower binding affinity for NMDARs, (R)-ketamine has a stronger and longer-lasting antidepressant effect than (S)-ketamine in preclinical models. Interestingly, mTORC1 is not as strongly activated by (R)-ketamine. Rather, its effect is thought to be through activation of extracellular signal-regulated kinase (ERK), highlighting the differences between the antagonists (Figure 1).[8]

Role of ketamine metabolites: hydroxynorketamine

Recent research has focused on ketamine and its metabolites, particularly (2R,6R)-hydroxynorketamine (HNK). Unlike ketamine, (2R,6R)-HNK activates AMPAR and regulates BDNF to produce potent antidepressant effects without significant NMDAR inhibition at antidepressant doses.[2,8]

In addition, the antidepressant effects of ketamine in animal models are abolished when the production of HNK is inhibited, supporting the idea that this metabolite is critical for the therapeutic efficacy of ketamine.[2]

Monoaminergic and dopaminergic modulation

Although not a conventional monoamine antidepressant, ketamine alters monoamine levels in the brain. In the prefrontal cortex, both (R)-ketamine and (S)-ketamine increase serotonin levels, but (S)-ketamine causes a greater release of dopamine. It's more pronounced adverse effects, like dissociation, could become worse. However, since ketamine is effective even when serotonin levels are low, these changes do not appear to be essential for its antidepressant mechanism.[8]

Lateral Habenula and burst firing inhibition

Another compelling theory involves ketamine's activity in the lateral Habenula (LHb), a region involved in encoding unpleasant stimuli. Abnormal bursting firing of the LHb has been linked to symptoms of depression. By inhibiting NMDARs in this area, ketamine reduces abnormal bursting firing and ameliorates depressive behavior in preclinical animals.[2]

ADDICTION

A neuropsychiatric condition that is persistent and recurrent, addiction has a substantial negative impact on society and health. For several substances, especially stimulants and cannabis, traditional pharmaceutical treatments have proven ineffective; relapse rates within a year of therapy range from 40% to 80%. Depending on dosage, frequency, and preparation, ketamine has revealed itself as a potentially neurotoxic medicinal drug. Despite being used in emergency anesthesia, it has been praised as a cutting-edge addiction treatment, but is infamous for causing severe neurotoxicity.[4]

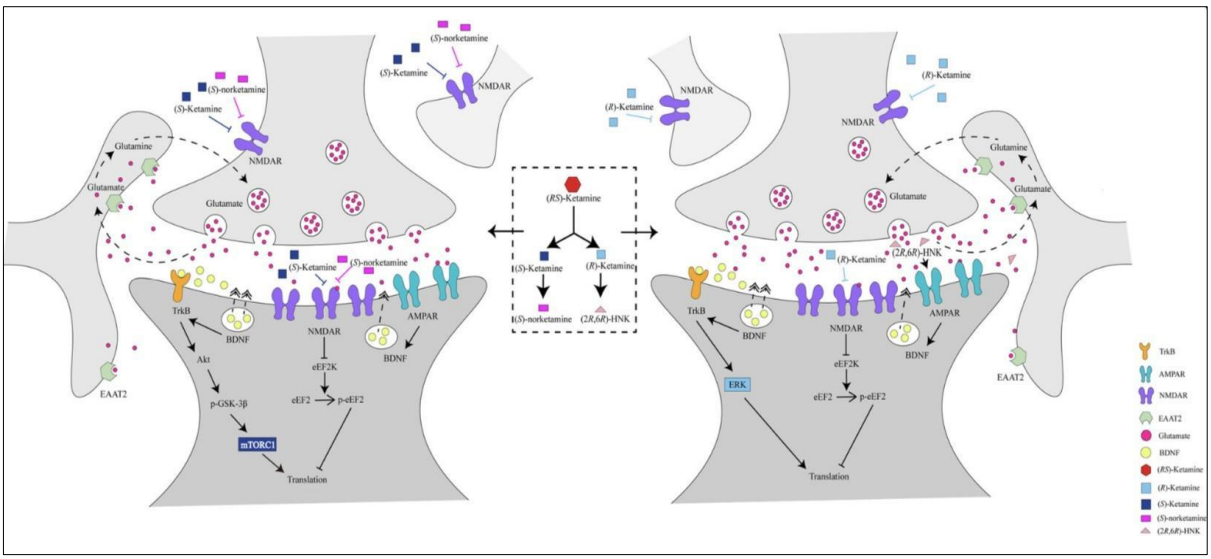

Figure 1: Proposed cellular mechanisms of antidepressant actions of enantiomers of ketamine and its metabolites. Left: (S)-Ketamine is metabolized to (S)-norketamine. (S)-Ketamine activates AMPAR, subsequently, (S)-ketamine activates mTORC1 signaling, resulting in activation of BDNF-TrkB signalling. Although (S)norketamine does not activate AMPAR, (S)-norketamine activates mTORC signaling, resulting in activation of BDNF-TrkB signaling. Right: (R)-Ketamine is metabolized to (2R,6R)-HNK. Antidepressant-like effects of (R)-ketamine in rodents are more potent than (S)-ketamine, and antidepressant-like effects of (2R,6R)-HNK are inconsistent. (R)-Ketamine activates AMPAR; subsequently, (R)-ketamine might activate MEK-ERK signaling, resulting in activation of BDNF-TrkB signaling.AMPAR activation may be necessary for antidepressant-like actions of (2R,6R)-HNK. The mTORC1 signaling and BDNF-TrkB signaling may play a role in the antidepressant effects of (R)-ketamine.

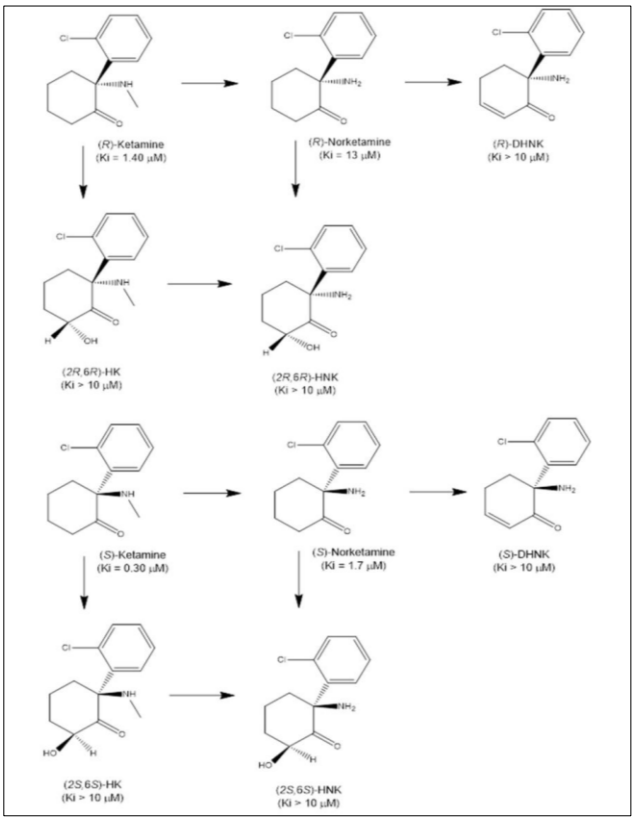

Figure 2: Chemical structure of enantiomers of ketamine and its metabolites. (R)-ketamine [or (S)-ketamine] is initially metabolized to (R)-norketamine [or (S norketamine] by either CYP2B6 or CYP3A4, and then metabolized to (R)-dehydronorketamine (DHNK) [or (S)-DHNK]. Hydroxylation of (R)-norketamine [or (S)-norketamine] at the sixth position by CYP2A6 results in (2R,6R)-hydroxynorketamine (HNK) [or (25,6S)-HNKJ. (R)-ketamine [or (S)-ketamine] is also metabolized to (2R,6R)-hydroxyketamine (HK) [or (25,65)-HKJ, then to (2R,6R)-HINK [or (25,65)-HNK]. The values in the parentheses are the Ki value for the NMDAR.

Ketamine addiction, although less widespread than opioid or amphetamine dependence, is different in its pathogenesis. By interfering with NMDA receptor signaling, it impacts glutamate systems and causes compensatory alterations such as dopamine dysregulation and a lack of prefrontal control, which in turn reinforces the habit cycle. Additionally, ketamine-induced dependence is characterized by obsessive seeking even in the absence of pleasure, which is brought on by frequent users developing cue-specific memory responses. From a neurobiological perspective, addiction is linked to lower levels of BDNF and neurogenesis. It has been demonstrated that long-term ketamine usage lowers cortical and hippocampus BDNF, making relapse more likely.[4]

Psychiatric symptoms like anxiety, disorientation, visual hallucinations, and memory loss are linked to ketamine abuse. Chronic users' clinical MRI investigations have revealed lesions in the cerebellum, brainstem, frontal, occipital, and parietal cortices, as well as in the basal ganglia, which are important brain regions involved in cognition and emotional control. Notably, even with brief usage, early shrinkage has been observed in individuals who combine ketamine with ecstasy or amphetamines. MRI scans revealed a marked reduction in these individuals' upright rotation.[9]

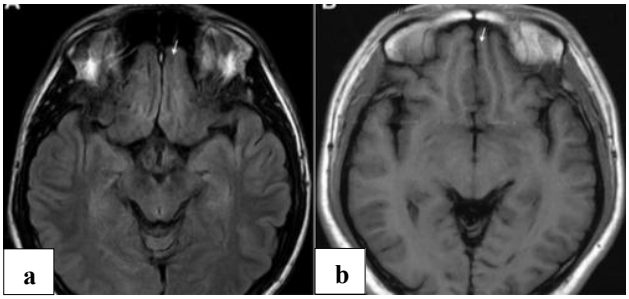

Figure 3: T1 images showed atrophic basal prefrontal (gyrus rectus) lesion of a 0.5-year-old ketamine addict who took three drugs, including (a) ketamine, and (b) control with no retraction of the gyrus rectus (arrow).[9]

Human MRI analysis confirmed widespread white and gray matter damage in ketamine addicts. Key findings included - year 1: hyperdense lesions in the superficial white matter, year 3: lesions extending to the internal capsule, year 4: degeneration of the basal forebrain, cerebellum, and pons diffusion blockage in the parahippocampal gyrus and insula, and tear 7+: degeneration of the striatum and midbrain (Figures 4-9).

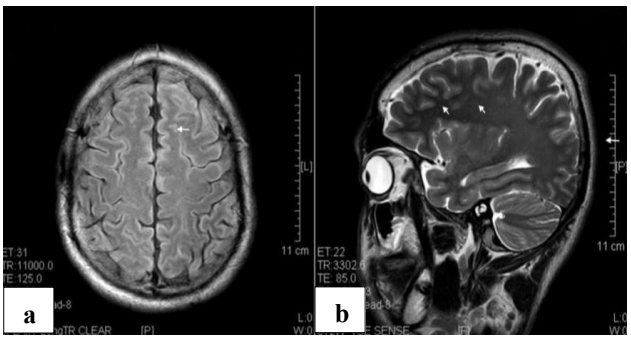

Figure 4: Hyperintense spots (arrow) in the superficial white matter and internal capsule of ketamine addicts, (a) FLAIR imaging of a 1-year ketamine addict, and (b) T2 imaging of a 3-year ketamine addict.[9]

The memory loss, anxiety, ataxia, and dyskinesia that chronic users experience are clinically linked to these structural abnormalities.[9]

Ketamine has demonstrated promise in treating addiction when administered under clinical supervision, despite its potential for abuse. Ketamine anesthetic treatment (KPT), a three-step procedure consisting of preparation, a guided intramuscular ketamine session, and post-session group

psychotherapy, was first proposed in Russia by Krubitsky and Grinenko. Compared to 24% of controls, 66% of alcohol-dependent patients in one of their investigations stayed abstinent after a year.

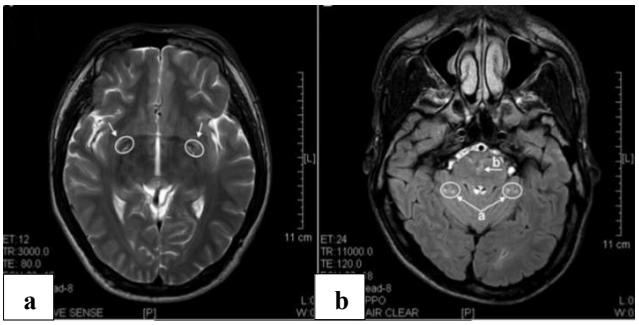

Figure 5: MRI images of the brains of a 4-year-old ketamine addict, (a) T2 image of a horizontal brain section showing degenerative hyperintense spots in basal forebrain (arrow), and (b) T2 image of a horizontal section showing hyperintense degeneration in cerebellum and in pons.[9]

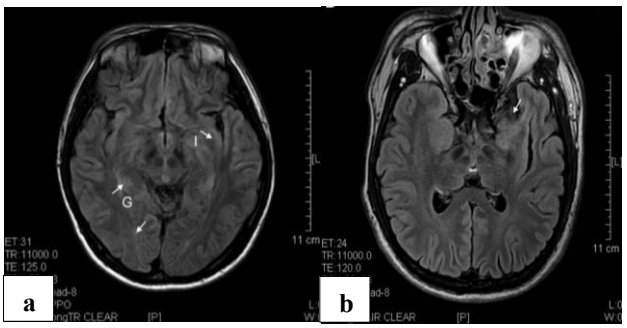

Figure 6: FLAIR image of diffusion blockage as hyperintense spots in the parahippocampal gyrus (G) and insula (I) as well as atrophy of uncus (arrow), (a) ketamine addict of 4 years, and (b) ketamine addict of 5 years.[9]

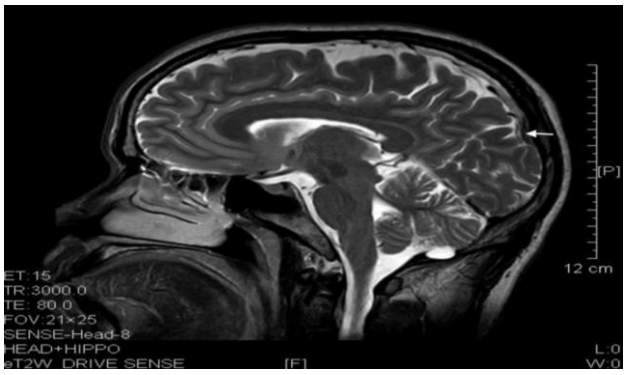

Figure 7: T2 image showed parietal atrophy (arrow) in a sagittal brain section of a ketamine addict of 4 years.[9]

High dose (3 g/day) included early prefrontal atrophy at 3 years (Figure 10).

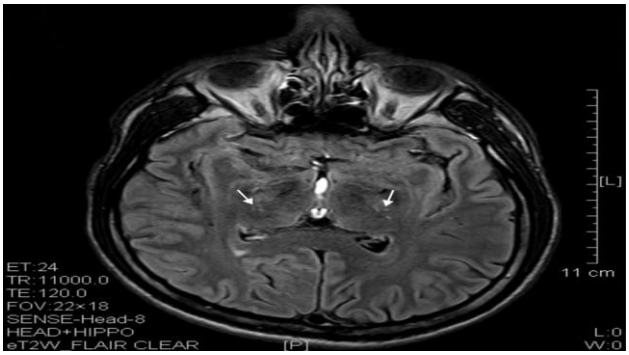

Figure 8: T2 image showed hypertensive degenerative spots in the corpus striatum (arrows) of a 6-year' ketamine addict.[9]

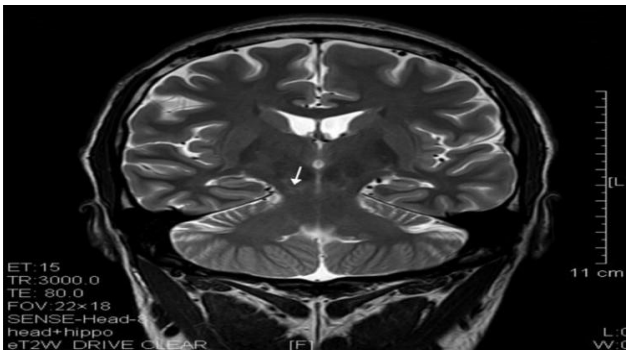

Figure 9: T2 image of a coronal section that showed a degenerative lesion (arrow) in the brainstem (midbrain) of a ketamine addict of 7 years.[9]

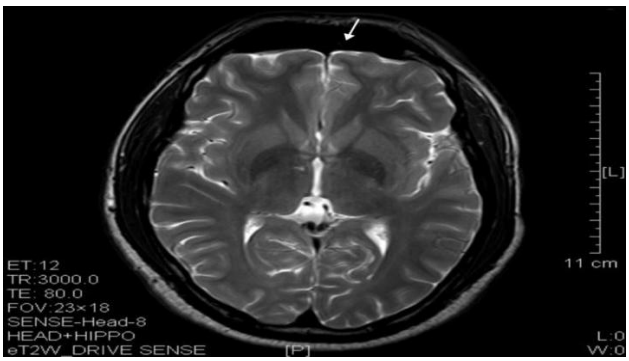

Figure 10: T2 image showed significant prefrontal atrophy (arrow) in a horizontal brain section of a ketamine addict who had a high dose of ketamine (3 g per day) for only 3 years.[9]

Dose-dependent efficacy has been demonstrated in other trials conducted on heroin addicts. In addition to showing less craving and more affective changes, patients who received 2.0 mg/kg of ketamine showed considerably higher abstinence than those who received 0.2 mg/kg. Ketamine infusions lessen craving and self-administration in cocaine addicts; these benefits are mostly mediated by mystical experiences rather than dissociation.[4] Reconnection with basic values, powerful symbolic

images, and sensations of regeneration are all reported by patients.[10]

Ketamine's advantages in addiction treatment include less frequent dosing, decreased stigma, and better patient compliance. Unlike methadone and naltrexone, ketamine is given in controlled, isolated sessions. The high comorbidity of depression and addiction makes the promise shown by intranasal administration significant. Nevertheless, many clinical trials are hampered by issues like inadequate randomization and active placebos, highlighting the need for more rigorous double-blind, placebo-controlled trials.[4]

TOXICITY

Because it is a non-competitive antagonist of NMDA glutamate receptors, ketamine is harmful because it disrupts these receptors, which changes perception, memory, and awareness.[5] Furthermore, ketamine's various physiological and psychological effects are explained by its interactions with other receptors, such as opioid, muscarinic, nicotine, and dopamine.[11]

According to studies, ketamine speeds up the heart rate and raises blood pressure by activating the sympathetic nervous system. Its cardiac depressing effects are obscured by these effects. It is also thought that the drug's wide tissue dispersion decreases the efficiency of dialysis in poisoning situations.[5]

Ketamine poisoning can cause mild to severe acute symptoms, such as dilated pupils, increased salivation, auditory and visual hallucinations, and awareness difficulties.[11] More severe side effects, like seizures, hypotension, and respiratory arrest, can happen, particularly if you take large doses or other depressants.[5]

The mainstay of treatment for severe poisoning cases is supportive care, which focuses on keeping the airway stable, keeping an eye on vital signs, and treating any neurological or cardiac issues as they arise. If there is no risk to the airway, activated charcoal can be utilized if ketamine has recently been consumed orally.[5]

Ulcerative cystitis, one of the most common symptoms among long-term ketamine users, is one of the major urinary problems linked to prolonged use. There have been reports of bladder wall alterations, reduced urine capacity, and symptoms such as hematuria, frequent urination, and abdominal pain.[6] Furthermore, ketamine can result in cholangiopathy, a condition that damages the liver and bile ducts and may necessitate surgery or the implantation of a biliary stent.[11] Chronic use has been linked to tissue alterations and inflammation in the kidneys and liver, according to clinical and experimental findings.[6]

Long-term use causes neurological side effects such as attention problems, memory loss, and psychotic symptoms resembling those of schizophrenia. These effects have been connected to dopaminergic system dysfunctions as well as alterations in the activity of the hippocampus, amygdala, and frontal lobe.[6]

The majority of research indicates that ketamine is safe when taken in prescribed dosages and under medical supervision, despite the dangers of using it outside of medical settings. Studies that examined incidents of poisoning and death have not found any deaths linked to its usage as an antidepressant. The World Health Organization has referred to it as one of the "essential" medications.[12]

These results are bolstered by data demonstrating that chronic ketamine use reduces synaptic proteins (e.g., Syn, PSD-95), resulting in measurable memory and learning problems.[13] Long-term users show cortical thinning, especially in frontal and parietal areas, according to human brain imaging.[14] High oxidative stress doses at the cellular level led to reactive oxygen species accumulation and neuronal apoptosis.[15] It seems that ROS/HIF-1α signaling is responsible for hippocampal degeneration.[16] Impaired spatial working memory and hippocampal abnormalities are functional consequences of ketamine misuse.[17] Brain scans show a correlation between cortical thinning and cognitive symptoms.[18] Irreversible prefrontal damage after chronic exposure in non-human primate models confirms these outcomes.[19] Studies at the molecular level show that ketamine-related cognitive deficits may involve changes in AMPA receptors on hippocampal neurons.[20]

CONCLUSION

Ketamine occupies a dual role as both a therapeutic breakthrough and a potential neurotoxic agent. This review underscores ketamine's rapid antidepressant mechanisms—primarily via NMDA receptor antagonism, AMPAR activation, mTORC1 signaling, and its metabolites like HNK—alongside its promising but complex application in addiction treatment. At the same time, chronic misuse poses significant risks to neurocognitive health, including structural brain damage and cognitive decline, particularly highlighted in regional contexts like Saudi Arabia where psychiatric uses are expanding. By integrating neurochemical, imaging, and clinical data, this article advances our understanding of ketamine's benefits and dangers, advocating for regionally tailored clinical guidelines, controlled usage, and continued research into long-term outcomes.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Albanna AK, Alnefaie ZM, Saleh AM, Alsayedeash FH, Almejmaj LS, Alturki AI, et al. Neurological effects of ketamine: mechanisms, addiction potential, and toxicity profiles with focus on Saudi Arabia. Int J Community Med Public Health 2025;12:3793-9.