



Review

Ketamine use disorder: preclinical, clinical, and neuroimaging evidence to support proposed mechanisms of actions

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ABSTRACT

Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, has been exclusively used as an anesthetic in medicine and has led to new insights into the pathophysiology of neuropsychiatric disorders. Clinical studies have shown that low subanesthetic doses of ketamine produce antidepressant effects for individuals with depression. However, its use as a treatment for psychiatric disorders has been limited due to its reinforcing effects and high potential for diversion and misuse. Preclinical studies have focused on understanding the molecular mechanisms underlying ketamine's antidepressant effects, but a precise mechanism had yet to be elucidated. Here we review different hypotheses for ketamine's mechanism of action including the direct inhibition and disinhibition of NMDA receptors, aminomethylphosphonic acid receptors (AMPA) activation, and heightened activation of monoaminergic systems. The proposed mechanisms are not mutually exclusive, and their combined influence may exert the observed structural and functional neural impairments. Long term use of ketamine induces brain structural, functional impairments, and neurodevelopmental effects in both rodents and humans. Its misuse has increased rapidly in the past 20 years and is one of the most common addictive drugs used in Asia. The proposed mechanisms of action and supporting neuroimaging data allow for the development of tools to identify 'biotypes' of ketamine use disorder (KUD) using machine learning approaches, which could inform intervention and treatment.

1. Introduction

Ketamine, a derivative of phencyclidine (PCP), was developed in the 1960s and released for public use in 1970 by the Food and Drug Administration (FDA) [1]. It is a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors and has been used primarily as an anesthetic agent in humans and veterinary medicine [2]. Ketamine was also approved by the FDA for treatment-resistant depression (e.g. esketamine), and has also been proposed for the treatment of bipolar disorder, anxiety, and chronic pain [3–7]. However, ketamine has reinforcing effects, inducing self-administration and conditioned place preference in rats, consistent with its potential for misuse in humans [8–11]. As a result, misuse of ketamine for its rewarding effects has grown significantly and gained popularity globally, and particularly throughout Asia, as a party drug. The 2019 World Drug Report by the United Nations Office on Drugs Control [12] classified ketamine under new psychoactive substances (NPS) that could pose a threat to public health and not under the control of international drug conventions. The prevalence of illicit

ketamine use varies from region to region with relatively low rates of 1.7% and 0.7% in the United Kingdom and United States, respectively [13–14]. However, in some Asian countries, ketamine is one of most used illicit drugs and was the primary NPS seized in 2019 in East-Asia [15–16]. Due to the illicit nature of the drug, precise numbers of people using ketamine may be higher than reported. The euphoric effects experienced at high doses known as the “K-hole” includes feelings of detachment from one's physical environment and losing sense of time, space, balance, and verbal skills, creating an “out-of-body experience”. The rapid brain uptake and fast emergence of its effects (duration up to 3 h) are believed to enhance the misuse and binge potential of ketamine; in support, ketamine users report the substance to be very addictive because of the short-lasting but euphoric effects; they also report chronic use is difficult to stop because it becomes a tool to engage in social interactions [17]. The lower price point of ketamine as a substitute for more expensive and less accessible drugs such as cocaine also might explain its growing popularity [18].

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Along with its high potential for misuse, both preclinical and clinical studies provide considerable evidence that ketamine misuse is associated with deficits in brain structure and function. Ketamine's effects appear to be largely mediated by the blockade of NMDA receptors, but it also has high affinity for dopamine (DA), serotonin (5-HT), glutamatergic, and GABAergic receptors. The precise mechanism of its pharmacological and addictive effects remains unclear. In this review, we will examine the various hypothesized models of ketamine's mechanism of action biochemically and behaviorally. These models are not mutually exclusive; thus, this review will use diverse models to support findings observed in recent clinical research studies. We also examine the ways ketamine affects neurocircuit structure and function in both preclinical and clinical studies. First, we aim to explain the structural and functional impairments observed in chronic ketamine use and examine the hypothesized mediating effects such as affective dysfunction, polysubstance use, pattern of use (i.e., frequency), and cognitive deficits. We also examine neurodevelopmental effects observed in preclinical studies and attempt to determine how well they emulate the clinical findings. Finally, we discuss recent findings of ketamine use as a research tool to model schizophrenia and critique the consistencies between clinical and preclinical findings to determine the extent to which these models are species-specific. Evaluating this literature is crucial to help identify potential early-onset markers and more effective treatments for ketamine use disorder (KUD). Since ketamine was developed in the 1960s, only studies from this time onward were searched. We reviewed original research articles using the database Pubmed and search engine Google Scholar. Additional references were identified from previous knowledge and recursive reference searching. Any research articles that focused on the neurological effects of ketamine before 1960 were excluded. The exclusion criteria were kept general to provide a broad and diverse understanding of the ketamine-induced brain changes.

2. Mechanisms of action

2.1. NMDA receptor antagonism

NMDA receptors are ligand-gated non-selective ionotropic glutamate receptors (iGluRs) and are essential to physiological roles in the central nervous system [19]. They are involved in the regulation of synaptic plasticity including long-term potentiation and long-term depression, which are vital for learning and memory [20–22]. Ketamine is a non-competitive NMDA receptor antagonist [23] that acts by blocking the flow of ions through the open channel [24]. This leads to the blockade of sensory inputs that manifest as schizophrenia-like symptoms [25–26]. However, these positive and negative schizophrenia-like symptoms seem to be present for both acute and chronic administration. With chronic use, these effects are long-term, persisting beyond the withdrawal period [27]. Within the last decade, ketamine has gained popularity for its fast-acting antidepressant effects which may be explained by several potential mechanisms on brain function in a dose-dependent manner. Subanesthetic doses (2 mg/kg) lead to low micromolar concentrations of ketamine in the brain that leave a large fraction of NMDA receptors unblocked [28–29], whereas anesthetic doses (10 mg/kg) block a higher NMDA receptor fraction [30]. Psychiatric effects have only been observed at subanesthetic doses [30–31].

Miller et al. [32] proposed two hypotheses for the antidepressant effects of ketamine: a disinhibition and a direct inhibition hypothesis. The disinhibition hypothesis suggests ketamine blocks NMDA receptors on GABAergic interneurons increasing aminomethylphosphonic acid (AMPA) receptor expression and upregulating glutamatergic synapses that results in cortical disinhibition, particularly in the prefrontal cortex (PFC) [33–34]. The direct inhibition hypothesis suggests ketamine inhibits NMDA receptors on pyramidal cells altering ongoing cellular pathways and triggering synaptic plasticity as demonstrated by evidence that deletion of GluN2B from cortical pyramidal cells mimics ketamine effects [35].

2.2. Monoaminergic systems

While ketamine appears to be largely mediated by NMDA receptor inhibition and subsequent AMPA receptor activation, recent studies have revealed that other pathways may also be involved. Kapur and Seeman demonstrated that ketamine has a direct effect on dopamine D₂ receptors and serotonin 5-HT₂ receptors [36]. A single subanesthetic dose of ketamine in rats led to a rapid increase in DA in the PFC of rats suggesting that repeated ketamine use could have a longer duration of effects on DA concentrations [37–38]. A PET imaging study in rhesus monkeys with continuous infusion of ketamine resulted in higher brain uptake of [¹¹C]-labeled cocaine analogs, [¹¹C]β-CFT and [¹¹C]β-CIT-FE, suggestive of an increase in brain dopamine transporter (DAT) availability by ketamine [39]. A recent study by Tan et al. explored the effects of ketamine in dopamine (PC-12) cells and nerve growth factor (NGF) to ketamine differentiated PC-12 cells resulted in decreased cell viability and increased DA efflux. In mice three months of chronic ketamine administration up-regulated DA synthesis enzymatic activity in the brain resulting in a delayed and persistent up-regulation of subcortical DA systems [40]. These results suggest that long-term ketamine misuse may lead to DA dysregulation in the CNS. Chronic ketamine misuse in humans was associated with up-regulation of D₁ receptor availability in the dorsolateral PFC, suggesting repeated recreational use may affect prefrontal dopaminergic transmission [41]. This upregulation may be driven by NMDA receptor blockade through D₁-NMDA receptor blockade coupling [42–43]. Like other substance use disorders (heroin, cocaine, and methamphetamines) D₂ receptor availability was lower in KUD when compared to controls [44–45]. This downregulation could be compensatory due to the chronic overstimulation of D₂ receptors following drug induced increases in synaptic levels of dopamine [46]. In contrast, D₁ receptor up-regulation is observed in ketamine and methamphetamine use disorder [41,45]. Worsley et al. suggest that the increase of D₁ receptors in methamphetamine use disorder may be attributed to a sensitization and positive feedback system as a result of prolonged dopaminergic stimulation. A similar mechanism might explain the up-regulation of D₁ receptors in ketamine users. However more research is needed to elucidate the mechanism underlying the upregulation of D₁ receptors in KUD and to assess if they recover with the prolonged discontinuation of drug use.

Ketamine has also been shown to bind to serotonin 5-HT₂ receptors and to inhibit the uptake of 5-HT in vivo [47]. Studies of subanesthetic ketamine doses showed increased release of 5-HT, noradrenaline, and glutamate [38,48–50]. 5-HT efflux in the medial PFC (mPFC) by ketamine has been associated with NMDA receptor blockade [37,48]. Subanesthetic doses of ketamine in the conscious monkey brain selectively enhanced serotonergic transmission by inhibition of the serotonin transporter (SERT) [51]. More recently, Lopez-Gil proposed that ketamine stimulates prefrontal glutamatergic projections to the dorsal raphe and the locus coeruleus, which in turn stimulate the release of serotonin and noradrenaline, respectively [52].

2.3. Dose-dependent behavioral impairments

Neurochemical changes are often related to behavioral and physiological changes observed with drug exposures of misuse. Ketamine tolerance builds over time in a dose-dependent manner due to its fast-acting effects [53]. Preclinical evidence and clinical case reports show that ketamine displays high risk for dependence, especially at high doses that contribute to the development of tolerance [54–58]. Over time there may be up to a 600% increase in ketamine dose needed compared to the one initially used [59]. With duration of use and increase in tolerance, there is a high potential for ketamine withdrawal upon cessation, with psychological symptoms similar to those from opiate withdrawal such as increased anxiety, depression, and craving [60–62]. However, in general physical withdrawal symptoms such as sweating, shaking,

and palpitations are not as prominent in ketamine dependence as with opioids and alcohol [56,59–60].

3. Baseline functional and structural impairments

3.1. Preclinical

Preclinical studies of ketamine have revealed significant changes in circuit function and structure including key regions typically thought of as central to the pathophysiology of drug addiction. Repeated ketamine exposure in non-human primates reduced functional activity in the substantia nigra, ventral tegmental area, and posterior cingulate cortex but increased activity in the striatum as assessed by blood oxygen level-dependent (BOLD) signal changes [63]. Ketamine also disrupted white matter microstructure across several circuits in non-human primates including fronto-thalamo-temporal and striato-thalamic connections, consistent with diffusion tensor imaging (DTI) findings in human chronic ketamine users [64]. White matter abnormalities have been observed in various substance use disorder populations [65]. A possible explanation for the observed myelin abnormalities could be a result of ketamine's neurotoxic effects as rodent and monkey research has shown neuronal apoptosis via the mitochondrial pathway when administered in high doses [66–68]. Another study revealed that ketamine exposure in mice over a period of six months resulted in neurodegeneration and hyperphosphorylation of tau proteins, which are hallmarks of Alzheimer's disease [69]. These preclinical studies highlight the harmful structural alterations that result from prolonged ketamine use.

In addition, repeated ketamine exposure induces persistent spatial working memory impairments that are evident for a prolonged period after acute drug withdrawal, suggesting long lasting alterations to PFC function [70]. Chronic administration of both subanesthetic and high doses of ketamine induce impairments in spatial learning, memory, and sustained attention in rodents [71–74]. Acute administration of PCP another NMDA antagonist drug with dissociative effects similar to those of ketamine reduced potassium-stimulated dopamine release in the PFC of rodents [75]. Working memory is heavily mediated by the PFC and modulated by dopamine suggesting that impairments could be a result of altered function of PFC neurons expressing dopamine receptors. Basal glutamate levels may also be involved in spatial and working memory impairments [76] and are reduced during repeated exposure of NMDA antagonists in rodents [75,77]. Studies have also demonstrated that repeated PCP exposure reduced the expression of GABAergic markers in the PFC of rodents, which is also critical in synchronizing pyramidal neuron activity in the PFC [78–80]. This GABAergic dysfunction may also play a role in working memory impairment. These findings suggest that ketamine's multiple mechanisms of action may all contribute to produce lasting neural alterations, with negative consequences to cognition and other behaviors.

3.2. Clinical

Chronic ketamine use in humans can cause global and regional brain neuroanatomical changes, some associated with other mediating factors. Structural MRI studies that evaluated gray matter and white matter volumes, and cortical thickness in chronic ketamine users found widespread reductions in prefrontal, parietal, temporal, left isthmus cingulate cortex, fusiform cortex, and lateral occipital cortices [81–85]. This global reduction is more severe with greater frequency of use [81]. To determine whether these observed structural impairments are specific to KUD, researchers evaluated the mediating effects of affective dysfunction and polysubstance use disorders. Chronic ketamine users, compared to chronic users of other recreational drugs exhibited larger surface area, cortical thickness and regional volumes in the striatum [81–82,86]. However, only the higher right caudate volume was associated with lower depressive symptoms in chronic ketamine users and in users who also chronically used stimulants [86]. The unique

structure-behavior relationship involving the striatum is consistent with ketamine's effects in dopaminergic function including its involvement with KUD [41].

Chronic ketamine use can also lead to alterations in functional connectivity in regions involved in processing drug cues. In a task-based fMRI study where participants viewed films depicting ketamine administration, sexual activity, and nicotine administration, chronic ketamine users compared to controls showed greater activation in the anterior cingulate cortex (ACC) in the ketamine film condition only [87]. Altered function of the subgenual ACC (sgACC) is associated with heightened depressive symptoms, and sex differences were identified in this circuit Li et al. Men had stronger functional connectivity between sgACC and bilateral temporal gyri associated with greater depressive symptoms, whereas women exhibited stronger connectivity between the sgACC and dmPFC in association with more severe depressive symptoms [64]. Clinical neuroimaging studies on depression often use the sgACC as the seed for functional connectivity analysis due to its role in affective processing and a primary target of brain stimulation therapies for treatment-resistant depression [88–90]. However, it is unclear if these results are specific to comorbidities of chronic ketamine use and depression, or if depression alone is driving this abnormal functional connectivity. Future preclinical and clinical studies should further explore the observed sex differences to support or challenge these findings. Functional connectivity of thalamic nuclei is also altered in ketamine misuse, which may be problematic because the thalamus plays a critical role in integrating learning and decision-making behaviors, and disrupted function is a behavioral marker for substance use disorders [91–92]. Compared to healthy controls, individuals who use ketamine chronically exhibited lower functional connectivity between the thalamus and PFC, posterior parietal cortex, the motor cortex/supplementary motor areas, and temporal cortex [93–94], which may be due to ketamine's antagonism of thalamic NMDA receptors [1]. In addition, striatal functional connectivity is altered in chronic ketamine users, which may relate to affective dysregulation. Consistent with preclinical evidence, chronic ketamine users exhibit striatal hyperactivity at rest. In humans, heightened BOLD activity was observed between the caudate nucleus and dorsal ACC, and between the pallidum and the bilateral cerebellum, relative to healthy controls [83]. A mediation analysis revealed that higher putamen-orbitofrontal cortex (OFC) connectivity is associated with greater self-reported impulsivity and longer duration of ketamine use. Interestingly, a study of individuals with opioid use disorder also observed a significant relationship between the striatal-OFC connectivity and self-reported impulsivity based on the Barratt Impulsiveness Scale, but in the opposite direction [95]. This altered pattern in connectivity in relation to impulsivity may be attributed to the maladaptive decision making and reward-associated behaviors observed in substance use disorders, however the directionality of the relationship should be further explored [96–97].

During spatial memory tasks, ketamine-dependent participants showed significantly lower activation of the right hippocampus and left caudate compared to healthy controls [98]. Based on preclinical findings it is speculated that these results are driven by neuronal apoptosis and upregulation of striatal D₁ receptors due to NMDA-R blockade [99–100]. Across preclinical and clinical studies, the consistency of these findings suggests spatial memory is clearly impaired in chronic ketamine users, however the evidence for other neurocognitive deficits is less robust. Ketamine-dependent participants have deficits in working memory and verbal learning, however, many studies cannot relate these behavioral impairments to differences in brain function or structure [85–86,101]. Foundational studies suggest that working memory, verbal learning, and verbal fluency are linked to frontal and medial temporal function [102–103]. Some speculate that the lack of a clear brain-behavior relationship underlying the cognitive deficits may be driven by compensatory mechanisms, including enhanced synaptogenesis to regulate excitatory input to pyramidal neurons following chronic NMDA receptor blockade from ketamine use [104–105]. Future studies could employ longitudinal

PET neuroimaging to better understand the brain-behavior relationships around chronic ketamine use and verbal learning/working memory impairments.

3.3. Neurodevelopmental effects of ketamine

Activation of NMDA receptors play an important role in neurodevelopment and disrupted NMDA receptor function is associated with several neurodevelopmental disorders [106]. Thus, it is important to consider the neurodevelopmental impact of ketamine on the fetuses of pregnant women who use the drug recreationally and on adolescent ketamine users, especially since ketamine is widely utilized and deemed safe as an analgesic and anesthetic in pediatric clinical settings, and adolescent ketamine misuse rates has increased in Asia over the past two decades [107–108]. Little clinical research has been done in this area in the context of recreational use, and therefore we review mostly pre-clinical studies that have investigated the impact of ketamine on brain development.

The neurotoxic effects of ketamine on development were first demonstrated by Ikonomidou et al. [109], with perinatal blockade of the NMDA receptors by ketamine leading to widespread apoptotic neurodegeneration in the developing rat brain. Since then, several rodent studies have investigated the different mechanisms and pathways underlying this developmental neurotoxicity [110–111]. Notably, ketamine exposure in utero leads to behavioral and cognitive deficits in rat pups, as well as impaired PFC development [112]. The developmental neurotoxicity of ketamine has also been demonstrated in non-human primates. Slikker et al. [113] found that ketamine-induced cell death in rhesus macaques was significantly greater when animals were exposed at gestational day 122 and postnatal day five than at postnatal day 35. Another study demonstrated that five hours of an hourly anesthetic dose of ketamine was sufficient to induce apoptosis in both prenatal (50–85 mg/kg) and neonatal (20–50 mg/kg) macaques, with effects being 2.2 times greater when ketamine was given prenatally [66]. Taken together, these results indicate that the neurotoxic effects of ketamine are dependent on the dose, length and developmental stage of exposure.

There are several potential molecular mechanisms for the neurotoxic effects of ketamine during development: modulation of NMDA receptors, induction of oxidative stress, and the disruption of neurogenesis. In response to ketamine exposure, NMDA receptors become overexpressed, leading to toxic intracellular calcium levels and the generation of oxidative stress in the mitochondria and dysregulation of markers of neurogenesis [110,114]. Numerous studies have demonstrated an upregulation of NMDA receptors in response to ketamine exposure. In an early study by Wang et al. [114–115], forebrain cultures were treated with ketamine, resulting in an upregulation of NMDA receptor expression. When 20 mg/kg of ketamine was administered to postnatal day (PND) 7 rats in six successive doses, NMDA receptor mRNA and subunit NR1 were upregulated compared to control rodents [72,114]. Importantly, the upregulation of NMDA receptors leads to the excitation of the glutaminergic system and acceleration of apoptosis in young neurons. This dysregulation may stem from ketamine NMDA antagonist effects while neurons are developing. In the same study by Shi et al. [72], NMDA receptor channel activity in forebrain slices of neonatal and adult rats exposed to varying concentrations of ketamine were measured using whole-cell patch-clamp recordings. Compared to adult neurons, neonatal neurons were more strongly inhibited at every concentration of ketamine, suggesting that immature neurons experience more extensive NMDA channel receptor blockade and may be more vulnerable to ketamine exposure during development.

NMDA receptor dysfunction also results in deregulation of neuronal calcium signaling and accumulation of toxic concentrations of calcium in the mitochondria. Increased expression of NMDA subunits leaves neurons more susceptible to the excitotoxic effects of glutamate once ketamine is cleared, leading to deregulation of calcium signaling and the generation of oxidative stress [114]. In ketamine-exposed forebrain

slices, higher levels of 8-oxoguanine production, an indicator for reactive oxygen species, were found in addition to elevated NR1 expression. Calcium imaging showed significantly higher levels of calcium influx and elevated calcium concentrations in neurons exposed to ketamine compared to controls [116].

A large concern for the presence of oxidative stress from ketamine exposure during neurodevelopment, particularly in the hippocampus, is the impact on learning and memory. Acute administration of ketamine in adolescent rats led to a decrease in spatial working memory and a reduction of anxiety-like behaviors. In addition, brain glutamate levels increased, along with oxidative stress as noted by increased plasma malondialdehyde and decreased antioxidant enzyme activity [116–117]. Early ketamine-exposed rodents (PND 7) showed significant learning deficits based on low performance on the Morris water maze and the passive avoidance tasks [118]. The deficits in memory and learning associated with ketamine exposure may stem from downregulation of the extracellular signal regulated kinase (ERK) signaling cascade [64,119]. Taken together, these results suggest that ketamine exposure during different periods of development leads to impairment in learning and memory via multiple molecular and cellular pathways.

Several studies have investigated the effect of ketamine on neural stem cells, with many noting dysregulated neurogenesis in the developing brain [120]. However, there are inconsistent results, with some noting increases and others decreases in neural stem cell proliferation in response to ketamine. This difference could stem from different methodologies, with some investigating neurogenesis in animal models like rodents, and others in culture cells. Preclinical evidence shows ketamine inhibits neural stem cell proliferation in the subventricular and subgranular zone, two key regions for neurogenesis in postnatal brains through a dose-dependent mechanism [116,121]. Migration of newborn neurons in the granule cell layer and growth of astrocytes in the hippocampus were also inhibited in PND 7 male rats [122]. More studies in this area are needed to determine the direction of dysregulation of neurogenesis caused by ketamine.

Clinical research on the neurotoxicity of ketamine exposure to pediatric populations is limited. However, Yan et al. [118] found that infants who received three surgeries under ketamine anesthesia had cognitive, language, and motor impairments following the final surgery compared to baseline measures. However, no significant differences between pre-and-post-operative performance were found among infant groups who received one or two surgeries under ketamine. In all three groups, the levels of S-100 β , a measure of central nervous system damage, were significantly elevated following exposure to surgical ketamine anesthesia at 8 mg/kg [118]. Moreover, in a clinical study by Bhutta et al. [123] investigating the potential neuroprotective effects of ketamine at a lower dose of 2 mg/kg against glutamate excitotoxicity, infants received either ketamine or placebo before cardiopulmonary bypass. While concentrations of C-reactive protein were lower in the ketamine group, no significant differences were found in the levels of various other biomarkers of inflammation/CNS injury or behavioral impairments. Clinical evidence for ketamine-induced developmental neurotoxicity is limited, though it is important to note that in each of these studies, ketamine exposure was minimized and used as a surgical anesthetic. Animal studies have indicated that prolonged ketamine administration increases its harmful effects, and while findings in animal investigations cannot reliably be extrapolated to humans due to interspecies variability, repeated and prolonged exposure should be more representative of regular recreational ketamine use [66,113].

3.4. Ketamine as a model for schizophrenia

Several studies have utilized ketamine as a model for schizophrenia in rodents [124]. Subanesthetic doses of ketamine produce schizophrenia-like symptoms, including dissociative states, cognitive impairment, and delusional thinking [125–126]. Ketamine's effects on glutamatergic and dopaminergic systems resemble those implicated

in the pathogenesis of schizophrenia. The dysfunction of NMDA and dopamine receptors seen in schizophrenia parallels that of ketamine: both chronic ketamine users and schizophrenia patients display upregulated D_1 receptor expression in the dorsolateral PFC, supporting the dopaminergic mechanism action of ketamine [41,127].

It is hypothesized that hyperdopaminergic signaling is responsible for the positive symptoms of schizophrenia, including delusions, hallucinations, disorganized speech, and catatonic behavior [128]. Ketamine may disrupt PFC function by interacting with dopaminergic transmission [38]. NMDA receptor dysfunction reduces the inhibitory control of PFC output neurons suggesting its role in schizophrenia [33]. As previously mentioned, ketamine's effects at NMDA receptors are complex. Magnetic resonance spectroscopy (MRS) and microdialysis suggest a net positive effect of ketamine on excitatory transmission via excessive glutamate release [129–131], which is hypothesized to drive the cognitive, morphological, and behavioral symptoms of schizophrenia [132]. Interestingly, administration of ketamine at anti-depressant doses appears to induce neurocircuitry changes linked to emergence of psychosis spectrum symptoms, and this may serve as a model of schizophrenia in humans [31,133–135]. Following a long-term intravenous infusion (45 mins - 1 hr) at a dose (0.3–0.5 mg/kg) close to that of the antidepressant uses of ketamine, healthy volunteers exhibited higher activation of the orbitofrontal cortex, pre-central gyrus, and paracentral lobule cingulate cortex in association with positive and negative psychosis symptoms [133–135]. The exact mechanisms driving the emergence of psychosis symptoms is unclear, but it seems clear that there is a high prevalence of psychosis spectrum symptoms among chronic ketamine users [25–26]. For instance, in 129 chronic ketamine users, 31.8% showed psychosis symptoms while only 20.9% exhibited depressive symptoms [136]. These findings underscore the need to better understand the link between ketamine and psychosis. Further, clinicians should be cautious when administering ketamine as an antidepressant in individuals who are at risk for developing psychosis.

4. Discussion

Given the increasing use of ketamine in Asia, there is a need for new tools that identify populations at risk of developing KUD. Diagnostic distinctions for substance use disorders (SUDs) typically rely on clinical symptoms and do not include the underlying neural correlates. There are currently no identified biomarkers of addiction that allow for the identification of relevant endophenotypes or clinical subtypes to influence personalized treatments [137]. However, it is well known that SUDs produce notable alterations in neural circuitry and structure. Machine learning of neuroimaging data possesses the potential to aid in the characterization of biotypes and endophenotypes specific to addiction, and for characterizing risk factors that may be used as biomarkers and allow for early intervention. This has been a promising approach in the mental health field in recent years, with a notable example being Drysdale (2016) who identified four biotypes of depression according to distinct whole-brain patterns of abnormal functional connectivity by using statistical clustering and fMRI [138]. In recent years, machine learning of neuroimaging data has also been applied to binge drinking behaviors and substance use disorders [139–142].

Several studies have demonstrated that these approaches can discriminate between substance users and non-users. Meier et al. and Jing et al. [143–144] have built models for predicting the risk of developing substance use disorders using risk factors from childhood to adolescence, such as adolescent use of tobacco and cannabis, childhood conduct disorder, and an early exposure to substances. Ruberu et al. [145] proposed a model to predict scores on quantitative measures of hazardous use of alcohol, cannabis, and tobacco from information about the individual's family and sociodemographic factors. Another model included neighborhood-level predictors (socio-demographic factors, drug use variables, and protective resources) to predict the location and risk of drug overdose [146]. Since SUDs are complex and often involve co-

morbid conditions, machine learning offers the unique promise of disentangling relationships that traditional statistical approaches could not uncover [147]. Though at this time we are unaware of any studies using machine learning for KUD, the rich investigations that machine learning affords make this a promising area for future investigation.

5. Conclusion

To date, there is no approved pharmacotherapy for KUD. Huang et al. [148] proposed the use of the antiepileptic drug, lamotrigine, because of its effect on glutamate release inhibition and a clinical case study where it reduced cravings. By evaluating the multiple molecular mechanisms of action, better interventions for KUD can be developed. This review addressed the ubiquitous mechanism of actions of ketamine, acutely and chronically in both medical and non-medical settings. The evidence discussed supports the neurotoxic, NMDA receptor antagonistic effects of ketamine. However, the downstream, dose-dependent effects on GABA, 5-HT, and dopaminergic systems, and how these may drive behavioral deficits in ketamine misuse remains under debate. Collectively these potential mechanisms may explain the reductions in global brain volumes and abnormal function and behaviors specific to KUD [81–85,87]. These results were most prominent in PFC regions, which is related to working memory impairments in rats following ketamine administration [70,75,78–79,83]. Working memory impairments are observed in human chronic ketamine users, but no association with altered brain structure or function, possibly due to enhanced synaptogenesis as a compensatory mechanism [85–86,101,104–105]. The discrepancy between the preclinical and clinical evidence may be due to preclinical studies mostly evaluating acute effects and clinical studies evaluating chronic effects, thus research on the acute effects of ketamine on working memory in humans ought to be explored before determining whether the preclinical evidence translates readily to humans. The impairments in working memory may be explained by dopamine and GABA dysfunction following acute and chronic ketamine administration [78–80]. Ketamine induces high rates of neuronal apoptosis and upregulation of D_1 receptors, potentially explaining hippocampal and striatal hyperfunctioning during spatial memory tasks following acute and chronic administration [73,98–100]. Neural and behavioral markers of ketamine administration are also evident at prenatal stages of neurodevelopment because immature neurons are sensitive to early ketamine exposure, resulting in dysregulated neurogenesis [72,118,120]. The molecular mechanisms of early ketamine exposure are potentially driven by the downstream effects of NMDA receptor blockade of oxidation stress and heightened glutamatergic, calcium and ERK signaling [110,114,149]. Heightened plasma levels of neuroinflammatory markers and neuronal apoptosis were related to cognitive impairments in clinical studies, supporting the behavioral relevance of these molecular changes [116–118,150]. Both preclinical and clinical evidence highlight striatal hyperfunction, which might be specific to KUD as compared to other drugs of abuse [63,151]. Striatal and PFC dysfunction are implicated in the positive and negative symptoms of psychosis from acute and chronic ketamine administration, presumably driven by hyperdopaminergic and glutamatergic signaling [33,128–131]. There is a lack of evidence on whether chronic ketamine users exhibit changes in brain function associated with the severity of psychosis symptoms. Thus, it is inconclusive if chronic ketamine use in humans induces markers of schizophrenia as in rodents. The studies discussed in this review revealed robust results for neurotoxic effects of ketamine, but they have several limitations such as low sample sizes, limited mediation analyses of behavioral variables, and limited inclusion of chronic ketamine users. There are important differences between the pre-clinical and clinical studies regarding the effects of chronic use on brain structure and function because the clinical studies obtained ketamine doses through self-reported responses, while pre-clinical studies administered ketamine in a controlled experiment. Thus, it is unclear how well the dose-dependent effects observed in the pre-clinical studies map on to the doses used in the clinical studies. Also, individ-

uals with KUD frequently used other drugs that might have interaction with the effects of ketamine in brain function. Future clinical studies should evaluate the influence of demographic factors such as age, sex and race/ethnicity, and changes in protein expression to analyze the synaptogenesis effects of ketamine. The application of machine learning approaches should also be considered for identifying risk factors, vulnerable populations, and biotypes to inform intervention and treatment of KUD. Further, a more diverse battery of psychological symptoms, behavioral measures, and brain structural/functional assessments in ketamine misusers will help clarify the precise mechanisms underpinning ketamine's diverse effects. The expansion of studies in this field is imperative since ketamine is increasingly being administered for medical treatment throughout the world.

Conflicts of interest statement

The authors declare no competing interests.

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Author contributions

Leah Vines: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Diana Sotelo:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Allison Johnson:** Formal analysis, Writing – original draft, Writing – review & editing. **Evan Dennis:** Formal analysis, Writing – original draft, Writing – review & editing. **Peter Manza:** Conceptualization, Writing – review & editing. **Nora D. Volkow:** Conceptualization, Writing – review & editing, Funding acquisition. **Gene-Jack Wang:** Conceptualization, Writing – review & editing.

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