BEYOND ANESTHESIA:
USES AND ACTIONS OF KETAMINE

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ABSTRACT

Background: Ketamine, first synthesized over six decades ago, continues to interest clinicians and fundamental researchers due to its multifaceted applications and complex mechanisms of action on the brain.

Aim of the study: This review synthesizes clinical and select preclinical studies to provide a broad overview of ketamine's clinical uses, with a particular focus on its expanding role in psychiatry. Despite its longstanding presence in the medical field, precisely how ketamine's effects on brain activity produce clinical benefit remains poorly understood.

Material and methods: The review begins with a brief historical account of ketamine's discovery and its evolution as an anesthetic and analgesic, setting the stage for its more recent advances and applications in treating psychiatric disorders. This review highlights a growing body of evidence supporting ketamine's use for certain psychiatric diseases, such as major depressive disorder, underscoring the drug's potential for reshaping therapeutic strategies. However, it also points to a significant gap in our understanding, for example, whether particular neurobiological mechanisms underscore ketamine's beneficial effects.

Conclusions: This review emphasizes the need for a cautious yet optimistic approach to integrating ketamine into clinical practice, balanced by the need to investigate its core neurobiological effects further.

KEYWORDS: ketamine, NMDA receptor, depressive disorder, brain, anesthetics, psychiatry

BACKGROUND

Ketamine, originally synthesized as an anesthetic, has become a compound of significant interest due to its diverse clinical applications, complex pharmacology, and profound neurobiological effects. Beyond its initial medical use, ketamine experienced a checkered history, gaining notoriety as a widely abused party drug in the 1980s and 1990s, which led to its classification as a Schedule III controlled substance. The turn of the century marked a pivotal shift in the perception of ketamine, driven primarily by its unexpected and rapid antidepressant effects in treatment-resistant depression.

AIM OF THE STUDY

This review examines ketamine's multifaceted roles, tracing its journey from its anesthetic origins through to its contemporary applications in treating resistant forms of depression and other conditions in the fields of psychiatry and neurology. By exploring ketamine's complex interaction

with brain connectivity and its impact on neuronal activity, we shed light on the mechanisms thought to underpin some of ketamine's therapeutic effects.

Material and methods

Ketamine: A historical overview

The history of ketamine traces back to the 1950s when the medical community sought safer alternatives to the prevailing anesthetics. A seminal report by Beecher and Todd, drawing from observations across ten prominent American hospitals, underscored the alarming anesthesia-related mortality rate of 1:1560 patients, spotlighting anesthesia as a significant health concern [1]. Against this backdrop, pharmaceutical companies embarked on an earnest quest for safer alternatives. On 26 March 1956, Parke-Davis synthesized CI-395, later recognized as phencyclidine [2]. Dr Edward F. Domino (1924-2021) conducted pivotal investigations on this compound in experimental animals, revealing its capacity to induce surgical plane anesthesia [3]. Encouraged by initial findings, the compound earned the moniker "Serynl" owing to the serene and tranquil states it seemingly engendered. In 1958, Parke-Davis, among others, initiated human trials for this compound. However, enthusiasm waned swiftly as it became evident that Serynl precipitated severe emergence reactions during the recovery phase from anesthesia, frequently manifesting as psychotic episodes and rendering patients unmanageable [4]. Owing to the prolonged emergence of delirium observed, Serynl was deemed unsuitable for human use.

The story could have ended there, but the program continued, and Parke-Davis researchers sought less potent PCP derivatives with more manageable side effects. They successfully synthesized a compound, approximately ten times less potent than PCP, which induced safe and short-lasting anesthesia in animals. This compound was known as CI-581, better recognized as ketamine. On August 3, 1964, the first human received ketamine via intravenous infusion by Domino and Corssen [5]. The most common side effect, during emergence, was feelings of out-of-body experience and being in a dream-like state. These effects were significantly milder than those produced by PCP, leading the FDA to approve the drug for human use. However, these psychoactive effects, along with the potential for abuse, prompted ketamine to be classified as a legally controlled substance. For a detailed personalized account by Domino of ketamine's discovery and initial research, refer to [6].

Pharmacological profile

NMDA receptor antagonism

Glutamate is the major excitatory neurotransmitter in the brain. It can bind to three different ionotropic receptors: NMDA, AMPA, and kainate receptors, which are expressed ubiquitously in the brain. Glutamate binding at these receptors produces a conformational change leading to the opening of the ion channel, allowing positive ions to move across the neuronal membrane, resulting in depolarization of the neuron. Ketamine is a noncompetitive antagonist at the NMDAR, binding to a distinct site inside the NMDA pore to block ion movement across the membrane. At rest, Mg^{2+} ions block the NMDA receptor channel, preventing activation; however, upon depolarization, Mg^{2+} is removed, enabling ion passage. Calcium influx through NMDA receptors is crucial for plasticity associated with learning and memory, so blockade of these receptors can significantly affect cognition by reducing NMDA receptor-mediated glutamatergic transmission. Other pharmacological agents, such as PCP or dizocilpine (MK801), can also block NMDA receptors, mimicking the effects of ketamine. Ketamine also interacts with AMPA and kainate receptors, which play roles in modulating synaptic transmission, plasticity, and neurodevelopment, but to a lesser extent than NMDA receptors [7].

Non-glutamatergic receptors

Apart from interacting with glutamatergic receptors, ketamine exhibits interactions with various other receptor systems, underscoring its complex pharmacology. As a pharmacologically active drug, ketamine can modulate serotonin 5HT-3 receptors, acting as a potentiator [8] and neuronal acetylcholine receptor subunit alpha-7 (CHRNA7), where it acts as an antagonist [9]. Additionally, ketamine influences several other receptors, including antagonistic actions at neurokinin 1 receptors (NK1) by interfering with the binding of neuropeptide substance P [10], 5-hydroxytryptamine receptor 1 (5HT1A) [11], 5-hydroxytryptamine receptor 2 (5HT2A) and dopamine D2 receptors (D2R) [12]. Ketamine also interacts with kappa-type (κ-), delta-type (δ-), mu-type (μ-) opioid receptors [13], and muscarinic [14] and nicotinic acetylcholine receptors (mAChRs) [15]. Ketamine can also inhibit several enzymes, such as cholinesterase [16] and also act as an inhibitor of sodium-dependent noradrenaline transporter [17].

HCN channels

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels play crucial roles in various functions, including synaptic plasticity, heart rhythm regulation, sleep regulation, and modulation of dopamine neuron activity. Recently, several investigators (Chen and colleagues [18] first identified in HEK cells; Zhang et al. [19]) have implicated HCN channels in the effects of ketamine. Subramanian and colleagues [20] have suggested that alongside NMDA blockade, antagonism of HCN channels is necessary for the functional effects of ketamine. Evidence supporting this notion comes from findings indicating that ketamine has a much weaker effect on HCN1 knockout animals. The authors proposed that ketamine may act as an antagonist for HCN channels in addition to NMDA receptors [21].

Downstream signaling

Since ketamine blocks NMDA receptors, this leads to disproportionate activation of AMPA receptors and their downstream pathways. There is evidence suggesting that AMPA receptor-mediated upregulation of mammalian target of rapamycin (mTOR), a kinase that regulates the initiation of protein translation and controls new protein synthesis, and brain-derived neurotrophic factor (BDNF), a protein linked with synaptic plasticity and the formation of synaptic connectivity, occurs after ketamine administration [22]. This is thought to promote the growth and maturation of dendritic spines as well as restore synaptic function [23]. Moreover, mTOR activity and BDNF expression can also be modulated by HCN channel activity, suggesting that several potential effector sites of ketamine could converge on the same downstream signaling pathways [24].

Clinical applications

Anesthesia

Anesthesia produced by ketamine was termed "dissociative anesthesia" — incidentally, it was Domino's wife who coined this term, which remains in use today. This description stems from the observation that patients under ketamine anesthesia appear detached from their environment. During anesthesia, their eyes may remain open, giving the impression of wakefulness, yet they are unable to respond to stimuli. Shortly after anesthesia, psychotic-like symptoms can occur. Neurophysiologi-

cally, the term "dissociation" was employed because researchers believed ketamine-induced dissociation between thalamocortical and limbic brain rhythms [25]. Today, ketamine continues to be utilized as an anesthetic in both children and adults, and it is considered effective in both induction and maintenance of anesthesia. The duration of ketamine anesthesia depends on the route of administration, typically lasting 20-30 minutes for intramuscular and 10-15 minutes following intravenous infusion. Importantly, ketamine does not induce respiratory depression, allowing respiratory drive and airway reflexes to function correctly. This characteristic is particularly advantageous, as it enables proper anesthesia for individuals with severe airway disease, severe burns, or status epilepticus [26,27]. Although clinically useful, emergence reactions occur during recovery in around 5-30% of patients, which has been highlighted as one of the major disadvantages of ketamine. However, these reactions can be effectively managed using benzodiazepines.

Depression

Ketamine's antidepressant effects were first observed in the 1990s in the USA. John Krystal, chief psychiatrist at Yale, noted rapid reductions in depressive symptoms among patients with treatment-resistant depression following ketamine intravenous infusions, at subanesthetic doses [28]. This finding initiated a wave of clinical and preclinical research in the field. While traditional antidepressants primarily target monoamine neurotransmitters like serotonin and dopamine, ketamine works by modulating glutamatergic neurotransmission and enhancing synaptic plasticity, offering a distinct approach to treating depression [29]. Ketamine exists as two enantiomers: S(+) and R(-). Esketamine is the S(+) enantiomer of ketamine and is the active ingredient in Spravato, exhibiting more effective antidepressant action compared to the R(-) enantiomer [30]. The nasal spray formulation Spravato was approved by the U.S. Food and Drug Administration (FDA) in 2019 for the treatment of depression in adults when two or more conventional antidepressants were ineffective. Ketamine is the first new type of antidepressant to be approved in decades. In clinical trials, reductions in depressive symptoms are observed within 24 to 72 hours after the first administration of Spravato, while classical antidepressants require a longer duration of treatment (early effects after 4-6 weeks of treatment) [31].

Subanesthetic doses of ketamine produce dissociation, short-lasting altered states of consciousness, sometimes described as mystical out-of-body experiences. Because of its side effects, ketamine must be

administered under the supervision of a healthcare provider due to side effects such as dissociation, sedation, and increases in blood pressure [32]. There has been a lot of discussion examining whether ketamine dissociation and antidepressant effects are causally related and, as stated in a recent review, "it remains unknown whether the dissociative experiences associated with ketamine administration represent a core feature of the antidepressant response or a side effect of a compound that will be minimized by future drug discovery efforts" [33].

Alcoholism

Although initial studies suggested that 3 mg/kg ketamine therapy for alcoholism may result in longer remission periods in patients [34, 35], later data have been equivocal, with some researchers observing no differences while others maintain that ketamine was beneficial, particularly when administered alongside benzodiazepines [36]. Studies have indicated that administering ketamine alongside benzodiazepines reduces the required dose for treatment [37]. A similar effect has been observed with lorazepam, where patients could receive smaller doses if ketamine was also administered. It is worth noting that all the aforementioned studies were conducted on relatively small groups of patients, so the data should be critically evaluated [38].

Obsessive compulsive disorder

The first major study on the effect of ketamine on obsessive compulsive disorder (OCD) was conducted by Rodriguez et al. in 2011 [39]. They demonstrated that 0.5 mg/kg ketamine may lead to the cessation of obsessive symptoms, but only up to a certain time point. Some symptoms had returned by 230 minutes following the second ketamine infusion, while the remainder reappeared seven days later. Further studies conducted by this group yielded mixed results. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) is used to assess the intensity of OCD symptoms. Following ketamine administration, patients' Y-BOCS scores decreased, including both compulsion and obsession scores. Currently available data suggests that ketamine holds promise in treating OCD symptoms; however, it must be administered repetitively over time [40] [41, 42]. Esketamine may be particularly promising; for example, in a case study by [43] involving a 28-year-old patient, the effects lasted at least 66 weeks. This, along with results from previous studies, may suggest that ketamine works best when combined with traditional therapy for OCD symptoms [43].

Posttraumatic stress disorder

Ketamine does not appear to be clinically useful in posttraumatic stress disorder (PTSD) or to be superior to midazolam. Several studies have shown a very small, often statistically insignificant, effect on patients suffering from this disorder. This effect seems to remain consistent over time, as results are similar 24 hours, 1 week, and 2 weeks after 0.5 mg/kg ketamine infusion. In fact, two studies [44, 45] have suggested that ketamine may even have a small negative effect on patients. However, ketamine, when administered as part of a therapy regime in certain cases, may facilitate PTSD treatment [46]. Despite ketamine's well-known dissociative effects, many studies have investigated whether ketamine may negatively affect PTSD patients. The majority of studies have concluded that ketamine does not appear to increase PTSD symptoms. PTSD is a complex condition, and it's important to note that it may be induced by a variety of distinct traumatic events, thus, the treatment approach may vary depending on the cause of the disorder [47].

Pain

Ketamine has been used as analgesic medication since the 1960s. Numerous studies have highlighted its beneficial effects on severe pain conditions, including neuropathic or postoperative pain [48, 49, 50]. Ketamine is a useful postoperative analgesic, as it reduces the need for opioid-based medication, which in turn lessens such postoperative symptoms as vomiting or nausea [20]. This has been observed in cancer patients and in people suffering from other diseases [51]. One such disease is complex regional pain syndrome (CRPS). Patients suffering from CRPS had decreased feelings of pain for up to 12 weeks post ketamine infusion. In some subjects, ketamine led to pain relief for as long as a few months. This, however, is most likely related to the number of infusions a patient was administered [48, 50]. Ketamine has also proven to be a beneficial analgesic for burn victims. A study done by Ward and Diamond has shown that despite a lack of comfort during infusion, it is most likely safe and effective for both adults and children [52,53]. Nevertheless, there are certain disorders for which the data is less favorable. Results from studies done on ketamine's pain relief in fibromyalgia patients have proven to be inconclusive. It also does not have any effect on phantom limb pain [54, 55].

Model of schizophrenia

The original studies of ketamine's progenitor, phencyclidine, noted that its effects were so intrigu-

ing that the term schizophrenomimetic was introduced to describe the impressive similarity of the effect of this drug and schizophrenia [56]. Today, ketamine is studied as a pharmacological model for schizophrenia. Studies involving ketamine have led to the "glutamatergic hypothesis of schizophrenia" [57], stating that the glutamatergic system is underactive in schizophrenia, which developed into the "NMDA receptor hypofunction model of schizophrenia" after the discovery of NMDA receptors [58, 59]. This is now supported by a wealth of molecular biology and genetic data showing that specific subunits of the NMDA receptor (NR1 subunit, both mRNA and protein and NR2C mRNA) were decreased in post mortem brains from people with schizophrenia [60]. From the genetic point of view, several susceptibility genes that have been associated with schizophrenia are linked with neuronal connectivity regulation and synaptogenesis. This includes genes for brain-derived neurotrophic factor (BDNF), dystrobrevin-binding protein 1 (dysbindin), neuregulin, disrupted in schizophrenia-1 (DISC-1), D-amino acid oxidase activator (DAOA), and regulator of G-protein signaling (RGS4) [61].

In humans, acute administration of subanesthetic doses of ketamine can produce both positive (delusions, paranoia), cognitive (disorganized thinking, formal thought disorder) and negative symptoms (social withdrawal, anhedonia) are similar to these observed in patients who suffer from schizophrenia. Long-term use of ketamine, in the case of individuals who have taken ketamine for several months, can produce a type of psychosis that is hard to distinguish from the initial symptoms of schizophrenia. The past decades have seen a substantial increase in fundamental research using experimental animals to understand how ketamine affects neurochemical, electrophysiological, and molecular changes in the brain. The goal of preclinical research is to understand how ketamine affects brain activity and, as such, potentially unveil the networks associated with psychoses.

Neurobiological Eefects

Ketamine disrupts the transfer of information between brain regions

Most anesthetics work by enhancing GABAergic inhibition, thereby suppressing the transmission of sensory information, such as pain, to the cortex as well as processing within the cortex. Ketamine, however, appears to work differently, and its mechanism remains poorly understood. One of the first ideas, postulated by Domino back in the 1960s, speculated that under ketamine, sensory input reaches the cortex but fails to be perceived by relevant association/

limbic areas [5]. Human electroencephalogram (EEG) studies have shown reduced fronto-parietal connectivity during ketamine anesthesia [62]. However, EEGs provide only an indirect measure of neuronal activity. More recently, electrophysiological studies using intracortical recordings in macaques have shown that during ketamine anesthesia, sensory information still arrives at the cortex; that is, sensory-evoked activity can still be recorded in the cortex but is not processed further downstream. In this way, ketamine can affect the processing of sensory information by reducing information transfer between regions [63].

In humans, ketamine-induced changes in connectivity between brain regions have been widely studied using a variety of different techniques, including EEG, functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG). The regions primarily targeted by ketamine seem to reflect the density of NMDAR and parvalbumin interneurons. One recent study found increased connectivity between basal ganglia and cortical networks, while decreased connectivity was observed between auditory and visual processing regions [64]. However, other studies have found changes in different brain regions, and there is a lack of clear consistency in the literature. This may be related to sample sizes, doses of ketamine administered, and the imaging techniques used; for example, see this review by [65].

Ketamine affects fundamental brain rhythms

Brain oscillations can be categorized on different frequency bands and associated with different brain processes. They are thought to subserve different functions, for example, slow oscillations are linked with promotion of restorative processes and facilitation of memory consolidation (delta, 0.5-4 Hz) or spatial navigation and episodic memory retrieval (theta, 4-8 Hz). Faster oscillations are associated with lower cognitive processes like attention, concentration (alpha, 8-12 Hz; beta, 12-30 Hz) or high-level cognitive functions (gamma, 30-100 Hz) [66].

Ketamine's impact on brain oscillations has been demonstrated in studies utilizing magnetoencephalography (MEG) and electroencephalography (EEG) in human subjects. One notable study by Rivolta investigated the effects of ketamine on resting-state brain activity recorded with MEG in healthy volunteers. Ketamine increased gamma power (30–90 Hz) in subcortical (thalamus and hippocampus) and cortical (frontal and temporal cortex) regions, while power of beta (13–30 Hz) was reduced in the precuneus, cerebellum, anterior cingulate, temporal and visual cortex. Additionally, connectivity analysis measured by transfer entropy showed increased information

transfer in a thalamo-cortical network after ketamine [67]. Other healthy volunteers' EEG study confirmed gamma (30–40 Hz) power increases and showed theta (4–8 Hz) power increases after ketamine [68]. Ketamine affects gamma oscillations in the frontal brain regions, which underlies its psychotomimetic and dissociative effects by alteration of neural synchrony and information processing [69]. The disruption of frontal gamma oscillations may result in a loss of neural network coherence and, as a consequence, mental disorientation, altered perception and the emergence of dissociative depersonalization symptoms. Shadli investigated ketamine's impact on oscillations in patients diagnosed with treatment-resistant generalized anxiety disorder and social anxiety disorder. Ketamine decreased delta (1–3 Hz) power and increased gamma (41–53 Hz) power [70] consistent with previous studies obtained by Hong [71]. In another study, unmedicated subjects with major depressive disorder (MDD) were treated with ketamine. MEG showed increases in gamma power (30–50Hz) after ketamine. Further, baseline gamma power was found to moderate the relationship between post-ketamine gamma power and antidepressant response [72]. Ketamine also increases theta and beta power, which may reflect alterations in arousal and attentional processes, enhancing dissociative experiences [68, 73]. Ketamine's effects have been well-investigated using experimental animals where recordings from electrocorticograms and local field potentials from deep brain structures can be carried out in a relatively straightforward manner, for here see here for a review [74].

Default mode network

The default mode network (DMN) is a group of interconnected brain regions that exhibit increased activity during introspection, self-reflection, and when detached from the external environment. It is often associated with mind-wandering and daydreaming. The DMN becomes less active during vigilance and goal-directed behavior, but enters a quiet waking, or "default," mode when individuals are not engaged in external activity or focused attention. Functional magnetic resonance imaging (fMRI) is a non-invasive method used to investigate functional connectivity between brain regions in humans. Overactivity of the DMN has been linked to mental illnesses, especially those characterized by excessive introspection, negative self-talk, worry, and anxiety [75].

Several studies have demonstrated that ketamine can reduce activity in the DMN, primarily by decreasing connectivity between key structures [76]. While there is ongoing debate about which brain regions constitute the DMN, the prefrontal cortex, cingulate,

and parietal regions are generally considered important players. Of note, the cingulate is widely regarded as a significant node in the DMN and is implicated in depression, making it an important target for ketamine's actions [77]. However, our understanding of the DMN is still in its early stages, and not all studies have reported consistent findings regarding depression (increased DMN activity) and the effects of ketamine (decreased functional connectivity) [65, 78].

Ketamine switches cortical state

The effects of ketamine on cortical activity have been extensively explored in experimental animals, where it is relatively straightforward to directly assess neuronal activity. Recently, using freely moving mice, a single injection of ketamine was shown to induce a rapid reorganization of brain activity. Ketamine reduced the firing of neurons that are typically active and increased the firing of neurons that are usually silent. This modulation of neuronal activity was observed across various cortical regions and layers, suggesting that it may underlie the transition from a normal waking state to a ketamine-induced "dissociated" state. The cortical network activated by ketamine may not only facilitate dream-like states but also contribute to some of the therapeutic effects of the drug [79].

Within the cortex, excitatory pyramidal neurons transmit information to their target brain regions, and the activity of these neurons is modulated by local inhibitory interneurons. Bita Moghaddam, Professor of Behavioral Neuroscience at OSHU, carried out pioneering work using freely moving rodents and demonstrated that NMDA antagonists (like ketamine) preferentially decrease the activity of cortical interneurons thereby reducing the inhibitory drive of pyramidal neurons [80]. This phenomenon, known as disinhibition, has been extended, showing that SST and PV interneurons, in particular, are a target for ketamine and that ketamine's actions at both NMDA and HCN1 channels appear important. Direct investigation in humans is limited due to the invasive nature of the techniques involved, ketamine has been shown to increase gamma band power, providing indirect evidence of cortical disinhibition [71].

Ketamine affects dopamine neurotransmission

In humans, there are some studies showing that ketamine may modulate dopamine neurotransmission; however, the results are not consistent. S-ketamine decreased [11] Craclopride binding potential significantly in the ventral striatum, followed by the caudate nucleus and putamen, indicating an increase

in striatal dopamine concentration [81]. In another study, ketamine significantly decreased dopamine receptor availability in the striatum, but this effect was not observed in the cerebellum. Furthermore, the cerebellar binding subtracted from the striatal binding was significantly reduced following ketamine administration [82]. These results provide support for the hypothesis suggesting ketamine's ability to increase striatal dopamine concentrations. However, they are inconsistent with other findings. For example, Kegeles evaluated the effect of ketamine on D2 receptor availability in subregions of the striatum (including the dorsal caudate, dorsal putamen, and ventral striatum). In this study, no significant differences were observed in D2 receptor availability measured before and during the ketamine infusion across any of the examined regions [83]. In line with the previous study, Aalto showed that ketamine did not alter striatal [(11)C]raclopride binding, which suggests that striatal dopamine release is of minor importance in the psychosis-like effects of ketamine [84]. Ketamine indirectly modulates dopaminergic neurotransmission, which has been shown in many rodent studies. Ketamine increases dopamine release in various brain regions, such as the prefrontal cortex, striatum and ventral tegmental area (VTA) [85]. This increase in dopamine transmission may contribute to ketamine's implication in cognition, mood regulation and reward processing. Reward processing may be affected dopamine modulation of the reinforcing effects of drugs of abuse and reward-seeking behavior. Dopamine dysregulation has been implicated in the pathophysiology of drug abuse, addiction and psychotic disorders [86]. Dopamine signaling is involved in the regulation of spinogenesis and spine morphology. Disruptions in dopamine transmis-

sion affect spinogenesis. Ketamine's ability to enhance dopamine release may promote spinogenesis and remodeling of dendritic spine density, leading to the formation of new synaptic connectivity and the restoration of synaptic plasticity in depression. Ketamine's interactions with dopamine receptors may also play a role in its antidepressant effects. In rodent studies, it has been shown that appropriate D1 receptor function is necessary to promote spinogenesis and rescue escape behavior after ketamine in the learned helplessness paradigm [87]. Modulation of dopaminergic neurotransmission by ketamine highlights the interconnections of glutamatergic and dopaminergic systems in the regulation of mental and behavioral functions.

Conclusions

Ketamine is a drug of complex pharmacology that has been of growing interest to researchers, pharmaceutical companies, and clinicians. Ketamine has transcended its original purpose, to emerge as a drug of considerable interest in the realm of psychiatry and neurology. Particularly noteworthy is the significant rise in ketamine's use in depression over the past two decades. However, the precise mechanisms underlying ketamine's dissociative and other psychoactive effects remain only partially understood. It remains unclear to what extent the dissociative effects may be an integral part, perhaps even the core, of ketamine therapy, or an undesirable side effect to be minimized during drug discovery. Comments made by Domino in his review a decade ago, emphasizing the need for further research [88], remain as pertinent today as they were then.

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