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New Frontiers in Ketamine Research: From Mechanisms of Action to Novel Psychiatric Treatment Approaches

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Abstract: Ketamine, initially developed as a safer alternative to phencyclidine, has emerged as a groundbreaking treatment in psychiatric practice. It gained popularity after its approval by the FDA in 1970 for its analgesic properties and ability to induce altered consciousness while maintaining vital functions. In the 1990s, researchers discovered its rapid and potent antidepressant effects, especially in patients with treatment-resistant depression. The mechanism of action of ketamine involves blocking N-Methyl-D-Aspartate receptors, leading to the release of inhibitory signals and increased glutamate levels. This process triggers a series of events promoting neuron growth and synaptic plasticity relevant to antidepressant outcomes. Various administration methods have been explored, including intravenous, intranasal, oral, subcutaneous, and intramuscular routes, each with its own advantages and limitations. IV ketamine administration has been widely used, but intranasal and sublingual forms are gaining popularity due to improved accessibility and safety. The FDA and European Medicines Agency approved intranasal S-ketamine for treatment resistant depression and depressive symptoms. Ketamine treatment is being extensively researched for its impact on various psychiatric domains, including resistant depression, suicidal crises, anxiety disorders, substance use disorders, and others. Preliminary evidence suggests potential benefits in conditions such as obsessive compulsive and personality disorders, although further research is needed. Ketamine's safety profile is generally favorable, with mild, temporary, and self-limiting side effects. However, caution is advised in individuals with uncontrolled hypertension, cardiovascular conditions, a history of psychosis, or substance abuse. Contraindications also apply to pregnant women. Ketamine interactions with other medications should be carefully considered, especially regarding benzodiazepines, and lamotrigine use. To optimize ketamine treatment in psychiatric diseases, guidelines recommend it as a third-line option after multiple unsuccessful antidepressant treatments for treatment resistant depression. Intravenous racemic ketamine has Level 1 evidence supporting its efficacy, while the evidence for non-intravenous formulations is limited. International guidelines vary slightly, but overall, the use of ketamine shows great potential in addressing challenging psychiatric conditions. This update highlights the expanding literature on ketamine in psychiatric treatment, focusing on its applications in treatment-resistant depression and its potential to revolutionize acute psychiatric emergency departments. Moreover, it provides insights into administration methods, safety considerations, and international guidelines for optimized ketamine usage in psychiatric practice.

Keywords: Ketamine, Psychiatry, Treatment Resistance

1. Introduction

Ketamine was synthesized in 1962 as a safer alternative to phencyclidine, with fewer adverse effects. [1, 2] Initial clinical trials confirmed its analgesic properties and ability to induce altered consciousness while maintaining vital functions. In 1970, it was approved by the FDA for use in humans and quickly gained popularity in clinical practice. [3]

In the 1990s, researchers began exploring ketamine's antidepressant properties and noticed mood improvement in patients, even when ketamine was administered for anesthesia. Subsequent studies in the early 2000s further confirmed its rapid and potent antidepressant effects, particularly in individuals with treatment-resistant depression (TRD). Ketamine demonstrated a significant reduction in depressive symptoms within hours or days, contrasting with the delayed response of conventional antidepressants. [4-7]

Ketamine's impact extends beyond depression, as it has been effective in treating symptoms resistant to other treatments, including suicidal thoughts, anxiety, and anhedonia. [8, 9] The antidepressant effects of a single dose of ketamine can persist long after its plasma levels decrease, suggesting the involvement of multiple cellular signaling pathways that enhance structural and functional plasticity relevant to antidepressant outcomes. [10]

While intravenous (IV) ketamine administration has been dominant, it requires medical supervision, resources, and costs. Intranasal and sublingual forms are gaining popularity due to their ease of administration and improved treatment accessibility. The FDA approved only an intranasal formulation of S-ketamine, branded as Spravato®, for TRD and depressive symptoms in adults with major depressive disorder. [11] The European Medicines Agency also approved it for similar uses. [12, 13]

Clinical studies and laboratory work have shown that sublingual (SL) transmucosal ketamine has a similar low-risk profile to intravenous (IV) ketamine, with excellent tolerance and rare side effects. [14] While SL ketamine administration requires a medicalized setting, it offers important benefits such as ease of administration, improved treatment access, and overall safety, making it a viable alternative for ketamine treatment. [15]

In this update, we highlight the main applications of ketamine in psychiatric treatment. The literature on "ketamine and psychiatry" is rapidly expanding, with over 500 publications per year. The focus primarily centers on treatment-resistant conditions, particularly depression, where significant success has been observed. Ketamine's anti-suicidal effects show promise and could bring revolutionary changes to acute psychiatric emergency departments.

Furthermore, we provide insights into different administration methods and compare the use of racemic ketamine with its enantiomers. Safety considerations, possible side effects, interactions, and international guidelines for ketamine usage are also discussed.

2. Mechanism of Action

The mechanism of action of ketamine is not fully understood, but it is believed to involve several processes. One proposed mechanism suggests that ketamine blocks N-Methyl-D-Aspartate receptors (NMDAR), which are receptors for the neurotransmitter glutamate, on γ-aminobutyric acid (GABA) interneurons. [16-18] This blockade leads to the release of inhibitory signals, allowing for an increase in glutamate levels. The increased glutamate activates a specific type of receptor called AMPA receptors, triggering a series of events including the upregulation of brain-derived neurotrophic factor (BDNF), which promotes neuron growth. [17] This process also activates downstream signaling pathways like the mammalian target of rapamycin (mTOR) pathway. [19, 20] Overall, ketamine is thought to reverse synaptic deficits caused by stress in the depressed brain by facilitating synaptogenesis and synaptic potentiation. [6, 12] This effect is particularly relevant in the context of TRD where synaptic impairments occur. [22]

S-ketamine and racemic ketamine primarily inhibit the NMDAR, but recent studies have identified additional mechanisms contributing to their antidepressant effects. These mechanisms include increased BDNF, activation of mTOR, and reduced inflammation. [23] Ketamine's anti-inflammatory effects provide a potential avenue for research and treatment, particularly in the context of depression and treatment resistance. [24]

Clinical research suggests that R-ketamine may have a milder side effect profile compared to S-ketamine while still reducing depression rating scale scores, as it has lower binding affinity to receptors associated with side effects, but recent randomized, controlled trials have not shown significant antidepressant efficacy of R-ketamine compared to a placebo. [24]

3. Administration

The administration of ketamine in psychiatric treatment is being extensively researched, with various routes including intravenous (IV), nasal spray (IN), oral, subcutaneous (SC), and intramuscular (IM) being explored, although the definitive efficacy and safety of these routes are not established. IV administration has the highest bioavailability, while IN and oral administration have lower bioavailability. [25, 26] In the case of IV racemic ketamine, repeated dosing is necessary for therapeutic benefits, with a recommended dosage of 0.5-1 mg/kg. [27] For IN S-ketamine, an induction phase of 4 weeks with a starting dose of 56 mg, administered twice weekly, is recommended. [28] Tablets have shown significant improvement in depressive symptoms with varying dosages and administration frequencies. [29, 25] IM and SC routes offer easier administration but have recommended doses ranging from 0.1 to 1 mg/kg. [25, 30] A meta-analysis compared IV, IN, and oral formulations of ketamine did not provide conclusive evidence on their comparative effectiveness. [26]

4. Psychiatric Domains of Application

Ketamine's antidepressant effects have positioned it as a critical treatment for TRD, leading to its exploration in various psychiatric domains, primarily in cases of treatment resistance, with studies investigating different combinations, dosages, administration routes, and practices, including IV racemic

ketamine as well as enantiomers and alternative forms of administration.

4.1. Resistant Depression and Other Affective Disorders

One of the most significant breakthroughs in ketamine research has been that ketamine can lead to rapid and significant improvement in depressive symptoms, including in cases of TRD [4, 5, 27, 28, 31-33] with probably less efficacy in elderly patients. [34] The antidepressant effects can be observed within hours and can last for several weeks, providing much-needed relief for individuals suffering from TRD. [25] The successful reduction of depressive symptoms is also observed in the presence of comorbidity with other psychiatric disorders or personality disorders. [35, 36] This is particularly important as psychiatric comorbidity has been associated with treatment resistance in MDD.

There is strong evidence indicating a persistent antidepressant effect of IV, and IN maintenance ketamine treatment with repeated administration in individuals with depression and TRD [25, 27-29, 38-40] Ketamine has demonstrated antidepressant efficacy in various stages of treatment resistance. However, as the number of failed treatment trials increases, the effectiveness of ketamine treatment may diminish. [41] Preliminary publications of ketamine-assisted psychotherapy (KAP) show promising results, [42] particularly with a specific improvement in sleep disturbances in TRD. [43] It is even considered meaningful to pursue ketamine therapy in cases where there is treatment resistance to electroconvulsive therapy (ECT) [44] or transcranial magnetic stimulation (TMS). [45]

To a more limited extent, there is evidence for sustained therapeutic potential of oral, IM, and SC maintenance ketamine treatment. [39] A recent observational study comparing IV racemic ketamine and IN S-ketamine in patients with TRD found no significant differences in effectiveness in terms of baseline-to-endpoint change or response/remission rates, but noted that IV racemic ketamine achieved remission faster based on the number of treatments, [40] while concerns about the efficacy and the short observation period for TRD were raised in high-impact factor journals shortly after the FDA approval in 2019. [46]

Currently, ECT is commonly recognized as a highly effective treatment for both resistant and non-resistant depression, although conflicting findings from recent meta-analyses suggest that ketamine may be equally effective [47, 48] or that ECT may have superior efficacy in reducing symptoms of non-resistant depression. [49]

Recent case studies have shown that ketamine treatment can improve mood and reduce psychotic symptoms in patients with TRD and psychotic features, [50] although the safety of ketamine in patients with psychotic depression remains a topic of debate, with limited studies showing no worsening of psychotic symptoms in TRD patients receiving ketamine infusions. [51] While concerns about potential manic episode exacerbation have limited the use of ketamine in bipolar depression, a large multicentric study demonstrated that ketamine treatment for treatment-resistant bipolar depression (B-TRD) is safe and does not significantly increase the risk of inducing a manic episode. [52, 53] But caution is advised in bipolar disorder type I without concurrent robust mood stabilizers. [54]

4.2. Suicidal Crises

There is strong evidence suggesting that ketamine has an anti-suicidal ideation (SI) effect, although it is not yet entirely certain whether the IN or IV form is more effective, as depicted below.

In a recent comprehensive analysis 12 randomized controlled trials were identified with reduction of suicidal ideation being the primary objective, while 14 trials had secondary objectives related to this outcome. [55] The results revealed that IV racemic ketamine exhibited superiority over control drugs, such as placebo or midazolam, within the first 72 hours, despite the presence of substantial placebo effects. Conversely, IN S-ketamine did not demonstrate any significant difference compared to placebo, [55] whereas SC racemic ketamine showed promising results. [56]

Overall, while IV racemic ketamine demonstrated efficacy in reducing suicidal ideation, particularly within the initial 72 hours, various research gaps and considerations remain. In a recently published review, it was found that both IV racemic ketamine and IN S-ketamine demonstrated a significant anti-SI effect. [57] Racemic ketamine showed a large anti-SI effect within the 4 to 6-hour timeframe and a medium-large effect within the 24-hour period. On the other hand, S-ketamine exhibited a small-medium anti-SI effect within the 4 to 6-hour timeframe and the 24-hour period. [57, 58]

4.3. Anxiety Disorders

In 2022, Tully et al. [59] conducted the first systematic review on the use of single-dose ketamine infusions for refractory anxiety disorders, which found significant positive treatment outcomes, including reduced irritability and panic symptoms, particularly with higher doses of ketamine administered weekly at 1 mg/kg, in patients with refractory anxiety disorders such as generalized anxiety disorder (GAD) and social anxiety disorder (SAD). [33]

In a recent meta-analysis, the first review to evaluate the effectiveness of ketamine in treating anxiety symptoms from a transdiagnostic perspective and using randomized control trials, it was found that ketamine exhibits rapid and long-lasting anxiolytic effects, starting within 3 to 4 hours after administration and lasting up to 2 weeks, providing reliable evidence while acknowledging remaining uncertainties in the literature. [60]

4.4. Substance Use Disorders

A review by Jones et al. [61] suggests that ketamine may enhance the ability to achieve and maintain abstinence in substance use disorders (SUDs), showing positive effects on cravings, motivation to quit, and self-administration in cocaine use disorder, as well as long-term improvements in alcohol and heroin abstinence. However, the reviewed studies

had limitations such as small sample sizes, limited demographic diversity, and inadequate control measures, highlighting the need for further research in this area. [61, 62]

More recent studies suggest that ketamine may have potential benefits as an additional treatment for severe alcohol withdrawal syndrome (AWS), with IV administration leading to decreased benzodiazepine requirements and early resolution of AWS symptoms. [63] Although ketamine showed improvements in abstinence rates and reduced alcohol consumption and cravings, the duration of these effects varied, and some patients resumed alcohol consumption. [63] While the effectiveness of ketamine in treating alcohol use disorders or withdrawal is still uncertain, [64] ketamine-assisted psychotherapy (KAP) has shown promising results in reducing alcohol use and the number of heavy drinking days. [65, 42] However, KAP may be more effective for SUD than for TRD, according to a systematic review of clinical trials. [66]

4.5. Obsessive-Compulsive Disorder

Few data are currently available regarding obsessive-compulsive disorder (OCD). Traditional treatment involves SSRIs or SRIs along with cognitive-behavioral therapy (CBT) and it has been demonstrated that ketamine may be utilized as an alternative treatment for mild and moderate OCD. [67, 68]

Approximately 25%-30% of OCD patients who do not respond to first-line treatment with SSRIs may undergo ketamine augmentation as a strategy after other interventions have proven unsuccessful. [69] Clinical trials indicate a rapid but temporary effect, lasting from days to weeks, with varying responses ranging from full remission to no significant benefit. [62, 68]

4.6. Personality Disorder

Fineberg et al. [70] published recently the first randomized controlled trial examining the effects of ketamine in individuals with borderline personality disorder (BPD). The study employed a double-blind, randomized controlled pilot design, enrolling adults with BPD who received either a single infusion of ketamine or a psychoactive comparator drug, midazolam. Both groups tolerated the infusions well, with no unexpected adverse events. However, participants who received ketamine reported more intense dissociative symptoms during the infusion compared to those who received midazolam, although these symptoms resolved within 40 minutes after the infusion in both groups.

Regarding the primary outcome measure of suicidal ideation and the secondary outcome measure of depression, the study found a numerical reduction in symptoms but did not observe significant differences between the ketamine and midazolam groups or across different time points. Similarly, no significant differences were found between the groups in terms of anxiety and BPD symptoms. However, there was a notable group by timepoint effect for socio-occupational functioning, with the ketamine group showing greater improvement than the midazolam group at Day 14. An exploratory analysis revealed a correlation between improvement in socio-occupational functioning and depression specifically in the ketamine group, but not in the midazolam group. [70] It appears that the overall severity of symptoms improves with the enhancement on the affective level, as observed in TRD with comorbid borderline personality disorder. [35, 36]

4.7. Posttraumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is characterized by a heightened state of arousal accompanied by intrusive thoughts, flashbacks, and nightmares. Animal studies have demonstrated the potential anxiolytic effects of NMDA antagonism using ketamine as reviewed by Liriano et al. [71]

Although there has been some hesitation in using ketamine for PTSD due to its potential to cause transient dissociation, recent studies indicate that this side effect may not be as common as previously believed [71] and various therapy settings are possible. One proposed mechanism for the beneficial effects of ketamine in PTSD is the upregulation of BDNF and the antagonism of NMDAR, which may help reverse some of the damage caused by chronic stress. [71] Ketamine may be more effective when used as a catalyst for psychotherapy rather than as a standalone treatment for mental health conditions [66, 72] even with oral S-ketamine in an outpatient setting. [73] The concept of KAP leverages its notable dissociative properties. When administered at low doses, ketamine can induce a feeling of detachment from bodily processes, allowing individuals to observe their mental experiences with greater openness and reduced defensive mechanisms. This dissociative state facilitated by ketamine may enhance the therapeutic effects of psychotherapy by providing a unique perspective and promoting self-reflection. [66, 74]

4.8. Eating Disorder

Recent studies highlight the association between anorexia nervosa and underlying dysfunctions in excitatory and inhibitory neurometabolite and signaling, with zinc deficiency being identified as a potential factor in the disorder's development due to its impact on glutamatergic and GABAergic signaling and NMDAR regulation. The novel combination of low-dose ketamine and zinc, through dual modulation of the NMDAR, shows promise in addressing impairments in executive control, reward processing, and interoceptive awareness, offering a targeted neurobiological approach for the treatment of anorexia nervosa. [62, 75]

5. Safety and Recommendations

5.1. Side Effects

The common acute side effects of ketamine and its enantiomers are generally mild, temporary, and self-limiting. These side effects may include dissociation, hallucinations, nausea, headache, elevated heart rate, and elevated blood

pressure. [76] Dissociation was found to be the most observed acute adverse event in approximately 15% of patients whereas hallucinations were reported as adverse events in less than 5% of the patients. [77] Clinical trials of IN S-ketamine have indicated that cognition generally remains stable or even improves over time. [38] The administration of IV racemic ketamine and IN S-ketamine should be carried out by healthcare professionals trained in cardiopulmonary resuscitation. Monitoring for 2 hrs. should include blood pressure, heart rate, respiratory rate, and oxygen saturation. The occurrence of cystitis has been reported with chronic uncontrolled or anesthetic doses of ketamine but has not been described with therapeutic dosages in the treatment of psychiatric disorders. [76]

Ketamine is known as a recreational drug, but it is consumed at approximately 10 times the dosage used in psychiatry. Therefore, its addiction potential is low at therapeutic dosage, and patients undergoing therapy do not report euphoria but rather dissociation. [76-78] Well-designed studies on the addictive potential in the context of psychiatric treatment with ketamine are not yet available.

5.2. Contraindications

While ketamine shows promise as a therapeutic agent, it is crucial to consider contraindications before administration. Ketamine should be used with caution in individuals with uncontrolled hypertension, history of psychosis, or cardiovascular conditions. Additionally, it is not recommended for use in pregnant women or those with a history of substance abuse. [76]

5.3. Medication Interactions

Ketamine is a lipophilic molecule primarily metabolized by cytochromes CYP3A4 and CYP2B6. Ketamine could induce CYP activity and could therefore also induce its own metabolism. [79]. The effect of a single dose on CYP activity in human is however unknown. Ketamine inhibits UGT enzyme [80], involved in the metabolism of selected drugs. Among these, morphine clearance is reduced by 50%, and increases rat brain morphine concentration. [81] Consequences in humans are not known, but caution is recommended. There is no significant interaction with medications used in the treatment of depression, particularly conventional antidepressants, lithium, and novel antiepileptic drugs. Conflicting and limited data exist with antipsychotics. [82] In contrast to previous findings, recent case reports have shown similar results for individuals who received a combination of racemic IV ketamine and a monoamine oxidase inhibitor (MAOI). [82, 83] Inhibitors or inductors of CYP can affect ketamine plasma levels and a formal interaction check is recommended. Common examples include clarithromycin (3.6 x AUC increase), clopidogrel and grapefruit juice. [84]

Clinicians have observed that coadministration of benzodiazepines with ketamine may alter its efficacy, likely due to increased inhibition of pyramidal neurons and counteracting the inhibitory effects on GABA interneurons mediated by ketamine's antagonism of extrasynaptic NMDAR, therefore, it is recommended to minimize the use of benzodiazepines in patients undergoing ketamine therapy for depression, [85] and while ketamine itself does not cause respiratory depression, it can potentiate the effects of other sedatives such as barbiturates, opioids, and alcohol. [14, 18]

Although there is limited evidence from controlled studies involving large patient groups, preclinical studies suggest that lamotrigine, by blocking NMDAR [86] and influencing neuroplasticity, synapse strength, and hippocampal lipid damage, [87, 88] may have the potential to enhance the antidepressant effects of ketamine and modulate cognition, while also reducing the side effects of ketamine and potentially decreasing ketamine cravings. [89]

5.4. Recommendations

Regarding ketamine treatment in psychiatric diseases, only recommendations for TRD are available, and even these guidelines are challenging to develop due to the lack of a universally accepted definition of TRD. The most used definition of TRD is based on the STAR*D Trial, which defines it as a therapeutic failure after two adequate antidepressant therapies. [90] This definition of TRD has received support from health authorities, including the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and the FDA in the United States. [11] However, achieving widespread acceptance of this definition has been difficult. One reason for this is the lack of standardized criteria for determining what qualifies as an adequate treatment trial failure. Additionally, there is debate about whether non-pharmacological treatments should be considered when considering TRD.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) established a task force to assess the evidence on the efficacy and safety of racemic ketamine and provide recommendations for its use in clinical practice. [14] Based on their review, IV racemic ketamine has Level 1 evidence supporting its efficacy in adults with TRD. The evidence for multiple infusions, whether given as an acute series or as ongoing maintenance treatment, is limited and corresponds to Level 3 evidence. Adverse events associated with ketamine infusions include both behavioral effects, such as dissociative symptoms, and physiological effects, such as hypertension. The evidence for non-IV formulations of racemic ketamine is limited, ranging from Level 3 to Level 4. Consensus recommendations have been provided for the clinical administration of IV racemic ketamine, which encompass various aspects such as patient selection, considerations regarding the facility and personnel, monitoring during treatment, and maintaining treatment response.

The British National Institute for Health and Care Excellence (NICE) has issued a recommendation stating that IV racemic ketamine treatment should only be considered after five consecutive unsuccessful treatments. [91] These treatments include two selective serotonin reuptake inhibitors (SSRIs), an antidepressant from a different class,

augmentation treatment, a combination of antidepressants, and ECT. Racemic IV ketamine should only be considered as a sixth-line treatment and exclusively for hospitalized patients. The NICE guidance published in January 2020 did not recommend the use of IN S-ketamine for TRD. According to the guidance, the drug should not be made available on the national health service (NHS) due to uncertainties regarding its clinical efficacy and cost-effectiveness. [92] In addition, despite receiving FDA approval in 2019, NICE does not recommend the use of S-ketamine for the treatment of MDD in adults at imminent risk of suicide.

Regardless of the differing recommendations mentioned earlier, an international group of mood disorder experts has compiled a synthesis of literature regarding the effectiveness, safety, and tolerability of racemic ketamine and IN S-ketamine in adults with TRD. They suggest utilizing ketamine as an augmentation treatment, considering it as a third-line option after two antidepressant treatments have proven unsuccessful. [28]

This update highlights the expanding literature on ketamine in psychiatric treatment, focusing on its applications in treatment-resistant depression and its potential to revolutionize acute psychiatric emergency departments, while also providing insights into administration methods, safety considerations, and international guidelines.

Conflict of Interest

There are no sources of support, the authors have no conflict of interest with any commercial or other associations, and no financial ties to disclose in connection with the submitted article.

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