EFFECTIVENESS OF KETAMINE IN THE TREATMENT OF MAJOR DEPRESSION: A REVIEW

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Abstract

Major depression or bipolar disorder is a serious global health and social problem that affects millions of individuals and has a major impact on their health and quality of life. Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) belongs to class of arylcyclohexylamine. This review went through the broad literature survey of article, published at various reputed platforms like Scopus, PubMed, ScienceDirect etc. demonstrating antidepressant action of ketamine in animal or human models. Ketamine is optical active whereas S (+) isomer is more active and potent but S (-) is less active and potent. The NMDA receptor, the opioid receptor, the monoaminergic receptor, the muscarinic receptor, and the voltage-sensitive Ca^{2+} ion channel are all targets of ketamine's interactions. Ketamine, in contrast to most other general anaesthetics, has no effect on GABA receptors. At low dosages, ketamine's antidepressant effects are apparent, and at greater doses, its psychotomimetic effects are mimicked, and finally, anaesthesia is induced. A single intravenous dosage of ketamine improved suicidal ideation and depression in a small study of 27 individuals with treatment-resistant depression in India. Although the effects of ketamine on depression are powerful and fast-acting. In 2019, the European Medicines Agency approved the use of the enantiomer of ketamine known as esketamine, also known under the brand name Spravato, as an antidepressant. In 2019, the United States and other countries approved esketamine as a nasal spray for treatment-resistant depression. In patients with bipolar depression, ketamine has been shown to alleviate symptoms 24 hours after administration, but not after 3 or more days. It concluded, that ketamine was found as effective antidepressant in lower does (≤10 times) that the dose used for the general anaesthesia. This study suggests to find out the leading mechanism of action behind its antidepressant action and to acknowledge the strategies to overcome the adverse drug reactions associated with the use of ketamine.

Keywords: ketamine, antidepressant, dissociative anaesthesia, NMDA-antagonist and rodents.

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Introduction

Major depression or bipolar disorder is a serious global health and social problem that affects millions of individuals and has a major impact on their health and quality of life [1]. According to the World Health Organization, depression is third on the list of leading causes of disability worldwide. Because of this, the societal price tag for disability will skyrocket [2].

More than 50 years ago, it was reported that the first patients had responded positively to a pharmacological therapy that modulated glutamate. Antibiotic cycloserine was first created to combat tuberculosis [3]. In 1959, Crane reported that cycloserine showed strong antidepressant effects when given to depressed individuals with tuberculosis, but it was also associated with serious adverse neuropsychiatric consequences [4].

Ketamine

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) belongs to class of arylcyclohexylamine. It is psychoactive substance that have medical and recreational applications. Ketamine is optical active whereas S (+) isomer is more active and potent but S (-) is less active and potent [5].

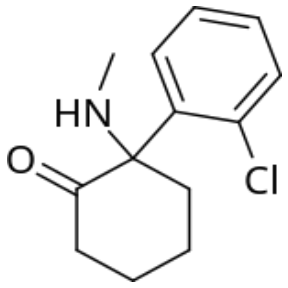

Fig 1. Structure of ketamine

Molecular formula : $C_{13}H_{16}C_lNO$

Molecular weight : 274.4g/mol

Ketamine was originally produced in 1962 as a phencyclidine derivative and tested on humans the following year. In 1965, researchers discovered that ketamine could be used as an anaesthetic, and by 1970, the FDA had authorised its usage in clinical settings [6][7]. Since then, ketamine's clinical utility has been expanded to include not only anaesthetic but also pain treatment and psychiatric uses [8]. Ketamine is the most widely-utilized anaesthetic and medically-relevant drug [9]. Pharmaceutically, it produces effects as varied as analgesia (both central and peripheral), sedation, bronchodilation, cataplexy, and stimulation of the

sympathetic nervous system [10]. Ketamine is a promising new treatment option with an almost instantaneous beginning of action, but there are few studies that have evaluated the effects of several doses of ketamine on depression and anxiety.

The NMDA receptor, the opioid receptor, the monoaminergic receptor, the muscarinic receptor, and the voltage-sensitive Ca^{2+} ion channel are all targets of ketamine's interactions. Ketamine, in contrast to most other general anaesthetics, has no effect on GABA receptors [11].

Ketamine, an NMDA receptor antagonist, also binds to the opioid beta and sigma receptors, making it a versatile drug. Dissociative anaesthetics like ketamine cause long-lasting analgesia and amnesia [12]. Ketamine has a lesser risk of respiratory depression and conserves airway reflexes more so than other anaesthetics [13]. There are several reasons why ketamine isn't widely utilised as an anaesthetic anymore, including its propensity for addiction and its unpleasant side effects i.e., euphoria, hallucinations, even panic attacks [14]. Ketamine, for instance, is used more frequently as a perioperative pain control tool than as a general anaesthetic induction agent [15][16].

In addition to its rapid solubilization in lipid and aqueous solutions, ketamine has a limited protein-binding ability [17]. This expedites the transport of ketamine through the blood-brain barrier, where it can reach concentrations 4- to 5-times higher than in the plasma [18]. As a result, the immediate analgesic action can begin working right away. Liver cytochromes CYP2B6, CYP3A4, and CYP2C9 convert ketamine to norketamine via ring hydroxylation and N-demethylation pathways and CYP2B6 and CYP2A6 metabolise norketamine further into 4-, 5-, and 6-hydroxynorketamine [18][19] Norketamine, the primary metabolite of ketamine, is less effective as an anaesthetic than ketamine. Its production begins shortly after intravenous ketamine and peaks around 30 minutes later. After being glucuronidated by the liver, norketamine is eliminated in the faeces, urine, and bile [20].

Increases in cardiac output, blood pressure, and heart rate result from ketamine's stimulation of the sympathetic nervous system. The sympathetic nervous system is activated by ketamine, resulting to elevated cardiac output, blood pressure, and heart rate. Ketamine should be used with extreme caution in people with ischemic heart disease [21].

Ketamine's solubility in both water and fat meant it could be given orally, intravenously, or intramuscularly. In order to get optimal plasma concentrations of the medicine, careful clinical thought must go into choosing the route of administration [22]. Intravenous or intramuscular administration of ketamine is common since these routes have the maximum bioavailability (100% & 93%, respectively) [23][24]. These options, however, may not always be viable depending on the situation (in critical care in children & obese patients). Oral, nasal, rectal, transdermal, sublingual, subcutaneous, and intraosseous delivery of ketamine have all been shown to be effective [25]. Recent research has established that the intraosseous route is a quick and secure way to administer ketamine [26][27]. This approach is particularly helpful for elderly patients, telemedicine, and preclinical emergency situations.

Dopamine transmission has been shown to be modulated by ketamine [28][29], but whether this is related to ketamine's antidepressant effect is unclear. Studies in both animal and human models of depression and studies of depression in both populations have linked ketamine to antidepressant effects [30].

Ketamine in the treatment of depression

Various scientists have shown the role of ketamine in the management of depression as enumerated below-

- Improving symptoms with pharmacotherapy that targets monoamine systems often takes between four and twelve weeks. N-methyl-D-aspartate receptors, in addition to serotonin receptors, have been shown to play a significant role in depression, according to recent research. They have been hypothesised to play a role in depressive states. In addition to its roles in neurodevelopment, neurocognition (memory acquisition), and neurotrophic function (nerve growth, differentiation, maintenance), glutamate is the primary excitatory neurotransmitter [31].
- At low dosages, ketamine's antidepressant effects are apparent, and at greater doses, its psychotomimetic effects are mimicked, and finally, anaesthesia is induced. Ketamine is a non-competitive voltage-dependent NMDA-receptor channel blocker [32]. A probable function in neuroplasticity is suggested by the fact that a single dose of ketamine has an immediate effect on depressed symptoms and that this effect lasts for up to a week. Remission of depressed symptoms was observed in many studies within a week after the infusion was administered. A meta-analysis demonstrated antidepressant efficacy from day 1 in both unipolar and bipolar depressive patients [33].
- In addition to alleviating depressed symptoms, ketamine's neuropsychiatric effects at subanaesthetic doses aid in the management of suicidal ideation and lessen the likelihood of self-harm or suicide [34]. Studies with no restrictions on the patients' identities have shown that a single dose of ketamine administered intravenously is effective in alleviating treatment-resistant depression, with the quickest significant antidepressant response being seen within 2 hours and the slowest within 4 hours [35].
- A single intravenous dosage of ketamine improved suicidal ideation and depression in a small study of 27 individuals with treatment-resistant depression in India [36][37]. To date, there have been no reports of serious physical side effects from the use of modest doses of ketamine or S-ketamine in antidepressant trials [38]. From its introduction to therapeutic practise, ketamine's antidepressant properties have been widely acknowledged [39].
- Ketamine is effective as both a mood lifts and pain reliever. Recent research suggests that hydroxynorketamine, a ketamine metabolite, is responsible for the drug's antidepressant effects. One meta-analysis found that ketamine effectively treated depression with a high response rate and quick effect. Ketamine has a rapid onset of action, alleviating depression in about 2 hours, when other antidepressants can take weeks to work [40][41]. Several case investigations came to the same conclusion, reporting that antidepressant effects of intravenous administration of subanesthetic

ketamine began within a few hours and persisted for 4-7 days. The promise of ketamine for treating depression that has not responded to other therapies is considerable.

- Although the effects of ketamine on depression are powerful and fast-acting [42]. Mood improvement after intravenous ketamine infusion for treatment-resistant depression may begin as early as 4 hours and reach a peak at 24 hours, according to a recent study [43]. Response rates greater than 60% as early as 4.5 hours post-dose (with a sustained effect after 24 hours) and greater than 40% after 7 days have been demonstrated following a single intravenous dosage of ketamine [44]. There have only been a small number of pilot trials conducted to determine the best dosage, but mounting data suggests that a dose of 0.5 mg/kg administered over 40 minutes produces the best results [45].
- Ketamine's antidepressant effects begin to wear off after 7 days, and most patients relapse within 10 days. However, for a sizable minority, the benefits can endure for 30 days or longer. A major difficulty with ketamine therapy is that its antidepressant benefits may not wear off immediately after treatment ends. Ketamine maintenance therapy, which typically occurs once every two weeks, is an option worth considering [46]. Suicidal ideation may be reduced for up to three days after a ketamine injection.
- A Cochrane review of randomised controlled trials in persons with unipolar major depressive disorder indicated that those treated with ketamine or esketamine had a reduction or remission of symptoms lasting 1-7 days, compared with those treated with placebo [47][48][49]. The 18.7% more persons reported some benefit, and 9.6% more people reached remission within 24 hours after receiving ketamine, compared to those who did not. At 24 hours, esketamine patients were more likely to have seen some relief (2.1%, 2.5-24.4%) and more likely to have experienced few or no symptoms (10.3%, 4.5-18.2%). Although the duration of the benefit is yet unknown due to the increased dropout rate in some studies, these effects did not last for longer than a week [50][51].
- In 2019, the European Medicines Agency approved the use of the enantiomer of ketamine known as esketamine, also known under the brand name Spravato, as an antidepressant [52]. In 2019, the United States and other countries approved esketamine as a nasal spray for treatment-resistant depression (Esketamine and Depression) [53][54]. Esketamine is a third-line treatment for depression, according to the Canadian Network for Mood and Anxiety Therapies [55].
- In patients with bipolar depression, ketamine has been shown to alleviate symptoms 24 hours after administration, but not after 3 or more days. Ten additional persons per thousand diagnosed with bipolar depression may have temporary improvement, but not complete resolution, of symptoms within 24 hours of starting medication. These projections are founded on the scant literature currently accessible [56][57].
- D-serine, a powerful co-agonist at the NMDA receptor, is of importance since it has been suggested as a potential therapeutic drug and/or biomarker in both depression and schizophrenia [58]. Researchers have shown that D-serine has antidepressant effects and that its levels may be aberrant in depressed individuals, based on findings

from both animal and human trials [59][60]. It's intriguing in this context that ketamine blocks D-serine transport, [61] that ketamine metabolites reduce intracellular concentrations of D-serine in PC-12 cells, [62] and that plasma D-serine levels predict a response to ketamine's antidepressant effects [63][64].

- Non-competitive antagonists at N-methyl-D-aspartate (NMDA) receptors are how ketamine and related arylcyclohexylamines work. This process in the brain and dorsal horn neurons is thought to be responsible for many of ketamine's therapeutic effects, including its anaesthetic, analgesic, and depressive qualities [65]. Several receptors and systems, including cholinergic, monoamine, purinergic, and adrenoreceptors, have been observed to interact with ketamine.
- Ketamine has antidepressant properties because it stimulates inhibitory serotonergic pathways that descend from the brain. Ten times lower amounts than required for anaesthetic purposes produce these effects. Ketamine's analgesic effects come from its ability to block both nitric oxide production and the central sensitization of dorsal horn neurons [66].
- The neurochemical effects of ketamine on depressed patients were also studied, albeit to a lesser extent. Rapid increases in plasma BDNF levels were observed in ketamine responders with TRD, although this conclusion was not supported by a different investigation. The studies cited above found that participants with higher BDNF levels also had milder depressive symptoms. Patients with a Val66Met single-nucleotide polymorphism, which has been linked to alterations in BDNF release and mRNA trafficking, also showed diminished responses to ketamine. The authors of a study on three ketamine-responsive depressive patients found elevated levels of plasma mTOR and eEF2 phosphorylation. While animal studies corroborate the increased mTOR activity, the reverse, an uptick in eEF2 phosphorylation, was unexpected. Pretreatment with rapamycin, a mTORC1 inhibitor, tripled the response rate at 2 weeks after treatment, as shown in a recent randomised controlled trial including 20 patients. Based on its immunosuppressive properties and its ability to promote homeostasis of synaptic density, the scientists hypothesised that rapamycin may have amplified ketamine's effects. Low-dose rapamycin has been shown to have enhancing effects by reducing inflammation in the periphery, but it is unclear whether it would reach sufficient levels to inhibit mTOR in the brain [67].
- The depressive symptoms can be quickly alleviated by ketamine, an N-methyl-D-aspartate receptor antagonist. Depressive and anxious symptoms were evaluated after being exposed to a subanaesthetic dosage of ketamine. Ketamine's effectiveness in reducing symptoms and easing suffering was evaluated. Twenty-five male patients with severe depression who had no history of psychotic condition, brain injury, organic disorder, cardiological problem, or substance addiction were admitted for the study. Ketamine hydrochloride injection was prepared and administered as a subanaesthetic intravenous bolus at a dose of 0.5 mg/kg. One hour following the initial dose, testing was performed again. During two weeks, six dosages were administered, and results were revaluated. Once 1 month had passed since the final dose, the results were considered final. Two weeks and one month following the last

dose of ketamine, there was a considerable reduction in depression, anxiety, and illness severity. Depression and anxiety, but not sickness severity, showed significant improvement within the first hour after the first dose. In a small number of patients, side effects were reported, however they were all mild and went away within an hour. The antidepressant effects of ketamine are both rapid and strong, appearing within minutes of the drug's administration and remaining stable beyond one month [68].

- A stronger antidepressant effect than a single ketamine was shown by the approach of repeated ketamine in open-label and saline-control studies of treatment-resistant depression. The consensus guideline also noted that there was a lack of evidence to justify the use of ketamine on a regular basis. Using midazolam as an active placebo, we evaluated the efficacy and safety of a single dose of ketamine to six repeated doses. The subjects were given either six doses of ketamine over the course of 12 days or five doses of midazolam followed by one dose of ketamine, with a post-treatment period of up to six months. The major outcome measure was the difference in MADRS scores between pre- and post-infusion days 24 and 48. Fifty-four out of a total of sixty participants finished all six injections. When comparing the six-ketamine group to the single ketamine group, there was no statistically significant difference in the change in MADRS scores at 24 hours post-last infusion, the primary end measure. After five infusions, repeated ketamine was more effective as an antidepressant than midazolam. Six ketamine was superior to a single infusion of midazolam in terms of remission and response following infusions 4 and 5. The median time to relapse among responders was marginally longer but not statistically significant (2 and 6 weeks for the single and six ketamine group, respectively). Overall, repeated infusions were tolerated reasonably well. After 5 infusions, ketamine was more effective than midazolam in treating depression, but this difference was not statistically significant when compared to the effect of adding a single dose of ketamine to midazolam [69].

Most studies on ketamine's neurochemical effects have been conducted in animals. It has been shown that ketamine stimulates glutamate release and neurotransmission in the rat prefrontal cortex (PFC). Co-administration of an AMPA receptor inhibitor reversed ketamine's antidepressant effects, suggesting that AMPA receptor activation is a key step in ketamine's mechanism of action.

Conclusion

Ketamine is a versatile medicine that has been utilised successfully in a wide range of clinical applications around the world thanks to its intricate mechanisms of action. Ketamine is now used more frequently for pain control and palliative care rather than just as an anaesthetic. It may be used alone or in conjunction with other medications. Ketamine is a viable substitute medication when pain is resistant to opioid and other adjuvant medicines since it has a powerful analgesic impact when given in modest dosages. In general, it can be said that while utilising ketamine may help chronic pain patients in the short term, there is little evidence to support its long-term advantages.

It concluded, that ketamine was found as effective antidepressant in lower does (≤10 times) than the dose used for the general anaesthesia. This study suggests to find out the leading mechanism of action behind its antidepressant action and to acknowledge the strategies to overcome the adverse drug reactions associated with the use of ketamine.

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Conflict of interest

Authors have confirmed for none conflict of interest.

Authors contribution

All the authors were equally contributed in the literature survey and writing of this review paper.

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