



## Ketamine: New Use for an Old Hat

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### Abstract

**Objective:** This article aims at examining the available knowledge about ketamine as a novel treatment option for management of treatment-resistant major depression.

**Method:** This is a non-systematic review utilizing search words 'ketamine' and 'depression'. Approximately 70 papers were reviewed of 1,800 papers that were identified in PubMed and Google Scholar.

**Results:** Multiple double blind randomized control trials demonstrated the efficacy of ketamine intravenous infusion in acute management of depression and treatment-resistant depression. Ketamine shows benefits in depressed mood within hours of its infusion and the effect is maintained for several days. Ketamine may also be associated with cardiovascular, neurological, psychotomimetic, and dissociative side effects.

**Conclusions:** Current data points to a rapid and robust action of ketamine as an antidepressant, even in treatment-resistant patients. Long-term efficacy and safety remain unclear. Available data are insufficient to recommend its routine use in clinical practice in psychiatry or its inclusion in guidelines for management of depression, but support ongoing examination of this anesthetic as an antidepressant treatment.

### Keywords

Ketamine, Depression, Antidepressant, N-Methyl-D-Aspartate (NMDA) receptor

### Introduction

Depression is one of the leading causes of disability not only in the US but worldwide as well. It is ranked third for global disease burden by the WHO [1] and estimated to affect 350 million people worldwide [1]. The economic burden of depression is estimated to have increased by 21.5% from 2005 to 2010 (from \$173.2 billion to \$210.5 billion) [2]. During an episode of depression, one may experience symptoms that are present most of the day, nearly every day. These include feelings of sadness, emptiness, or unhappiness; loss of interest in normal activities; sleep disturbances; tiredness and lack of energy; changes in appetite; and frequent thoughts of death and suicidal thoughts. Symptoms should be severe enough to affect functions of daily life [3].

Despite the clinical significance of depression, the pathophysiology underlining depression is still poorly understood. The monoamine hypothesis of depression enjoyed considerable support for more than 40 years; focusing on central deficiency of serotonin, norepinephrine and (to a lesser extent) dopamine. But it is clear that there are significant gaps in our understanding of

this complex disorder [4]. Most clinically available antidepressants act in different ways leading to increase the monoamine synaptic signal. Unfortunately, there is a lag of therapeutic effects and disappointing remission rates of the current available antidepressant treatments, leaving a significant unmet need.

For a couple of decades preclinical data has been accumulating in regard to the role of the glutamate system in the pathophysiology of depression [5]. It has been observed that patients with depression have higher plasma and CSF glutamate compared to controls [6,7]. Of the glutamate antagonists available clinically, ketamine seems to be the most promising. In the year 2000 Berman, et al. published an article about seven patients with

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treatment-resistant depression who were administered a ketamine intravenous infusion that resulted in significant improvement of their symptoms [8].

## Methods

Keywords of 'ketamine' and 'depression' were used in Pubmed and Google Scholar. The resulting 1,643 references in Pubmed, and the first 150 of the 93,000 references in Google Scholar were reviewed. Of these, papers describing controlled trials in the treatment of severe depression were examined. Since the purpose of this review was to provide a useful review for anesthesiology professionals, we did not perform a systematic review, but utilized important studies that edify regarding the use and consequences of ketamine in depressed patients. When available the Standardized Mean Difference (SMD) was included to allow for relative comparison the observed therapeutic effect between various studies [9].

## Ketamine

Ketamine (2-[2-chlorophenyl]-2-[methylamino]cyclohexanone) is an arylcycloalkylamine compound. It is structurally similar to Phencyclidine (PCP) and cyclohexylamine. The free-base form of ketamine is highly lipid soluble. It is commercially available as an aqueous preparation of the hydrochloride salt [10]. Ketamine can be administered via multiple routes, including oral, intravenous, intramuscular, subcutaneous, intranasal, epidural, transdermal, intra-articular, and sublingual [11].

Ketamine is a noncompetitive antagonist of the voltage gated N-Methyl-D-Aspartate (NMDA) receptor, inhibiting the influx of sodium and in the presence of the co-agonist glycine [12]. The interaction with multiple peripheral receptors is responsible for ketamine's transient cardiovascular, respiratory, and sympathomimetic side effects [13].

## Ketamine in depression

Berman, et al. [8] described the first study showing that ketamine is effective as an antidepressant when administered at subanesthetic doses. Subsequently, several studies confirmed this finding. One of the reasons ketamine is gaining a lot of attention is that it is the only treatment modality with ultrarapid response, as early as 2 hours [14]. Multiple meta-analyses have been performed showing a robust, yet transient, antidepressant effect of a subanesthetic dose of ketamine in patients with treatment-resistant depression [15-18]. The studies reviewed in this paper utilized the intravenous route of administration. While ketamine can be administered orally, it has much lower bioavailability (about 20%) [19]. This fact, coupled with the potential for abuse of prescribed ketamine, preclude routine oral use.

A meta-analysis performed by Lee, et al. in 2015 [20] (done using the data provided by the authors of the original manuscripts of 5 randomized placebo-controlled trials) showed a large and statistically significant antidepressant effect at 24 h post-infusion, with overall Standardized Mean Difference (SMD) of 1.01. The SMD allows for a relative comparison between studies that are statistically significant [9]. The effect size dropped from large to moderate at 7 days post-infusion. Fond, et al. [17] meta-analysis in 2014 included 9 randomized placebo-controlled trials, showed similar statistically significant results with overall SMD of 0.99. A Cochrane network systemic review in 2015 [16] was done using 25 double- or single-blind RCTs comparing ketamine, memantine, or other glutamate receptor modulators with placebo or other active psychotropic drugs, or Electroconvulsive Therapy (ECT) in adults with unipolar major depression; 1,242 subjects were included. Results showed that among all the glutamate modulators investigated only intravenous ketamine was more effective than placebo with odd's ratio of 10.77 at 24 hours (95% Confidence Interval [CI] 2.00 to 58.00), 12.59 at 72 hours (95% CI, 2.38 to 66.73) and 2.58 at one week (95% CI, 1.08 to 6.16) [16].

Since Ketamine can be used as an anesthetic, its use as part of the anesthesia administered for induction of seizure in ECT has been investigated. Li, et al. [20] performed a meta-analysis of 16 studies that investigated the efficacy of ECT plus ketamine plus other anti-esthetic agents, or ECT with other anti-esthetic agents in the absence of ketamine. There were 346 patients receiving add-on ketamine anesthesia in ECT and 329 controls. The addition of ketamine increased the antidepressant response significantly ( $p < 0.001$ ). This effect was seen if patients received either unilateral or bilateral ECT.

Most of the studies done with ketamine as a treatment for depression used subanesthetic doses at (0.5 mg/kg) infused usually over 40 minutes as the original work done by Berman, et al. [8]. More hemodynamic instability was noticed in patients with body mass index more than 30 kg/m<sup>2</sup> [21] requiring caution in this population or using lower dose.

## Side effect profile

As an anesthetic, a loading dose of 1.5 to 2.0 mg/kg IV in children or 1.0 mg/kg IV in adults over 30-60 seconds is usually given. An additional incremental dose of ketamine (0.5 to 1.0 mg/kg) may be used if initial sedation is inadequate [22]. Possible side effects include transient laryngospasm, transient apnea or respiratory depression, hypersalivation, emesis (usually in recovery), muscular hypertonicity, clonus, hiccapping, and recovery agitation [22]. Although ketamine has a direct vasodilata-

tion effect of vascular smooth muscles [23], the overall response to ketamine is sympathomimetic. Due to direct stimulation of central nervous system structures, ketamine result in increase in sympathetic tone with elevated blood pressure, heart rate and cardiac output [24]. When infused slowly, ketamine does not seem to produce any profound respiratory depression when used in anesthetic or subanesthetic doses [25], however, rapid administration may reduce respiratory drive. In animal models, low dose ketamine in anesthesia showed that it stimulates breathing, leading to higher flow-rate and respiratory rate [26]. In addition to stimulating breathing, ketamine also increases the genioglossus muscle tone [26] which can be protective to the patency of the airway during anesthesia.

At the subanesthetic doses (0.1-1 mg/kg) used to investigate ketamine's antidepressant properties, cardiovascular, gastrointestinal, neurological as well as mental status changes has been reported [21,27], therefore, adequate support is required during administration.

### Abuse potential

Ketamine is a known substance of abuse. Possibly due to its psychedelic like properties, and/or its agonist activity at mu opioid receptors, as well as increase dopamine release [28-30]. Early studies in depressed patients that specifically exclude patients with a history of substance misuse, have not demonstrated problems with abuse [21], but long term studies are still lacking. High doses of ketamine in rats (intraperitoneal 25-80 mg/kg) revealed evidence of neuronal degeneration and apoptosis [31]. Ketamine has been used widely in emergency room setting for pediatric age (usually between 4-6 years) for the past 4 decades with no human studies showing any evidence for apoptosis or neuronal degeneration [32]. No long-term neurodevelopmental follow up studies has been done to the author's knowledge which would be helpful as more conclusive evidence.

### Psychotomimetic and dissociative effects

The psychedelic like properties of ketamine has been known for a long time. Studies examining these properties showed psychotomimetic effects (conceptual disorganization, hallucinations, suspiciousness, and unusual thought content) and dissociative effects (objects seem unreal or moving in slow motion, alternation of visual or auditory perception or out of body experience) [21,33]. Dissociative and psychotomimetic (less common and severe) side effects were evident in studies using ketamine for depression in subanesthetic dosage [21,27]. These effects are usually transient and resolve with 4 hours of the infusion [21,27].

### Drug-Drug Interactions

Ketamine is metabolized through the hepatic cytochrome P450 enzymes (mainly 3A4) [34]. CYP3A4 in-

ducers like rifampin and St. John's wort can increase the metabolism and clearance of ketamine. Enzyme-inhibiting substances such as clarithromycin and grapefruit juice can prolong the half-life of the parent compound.

### Possible Mechanism of Action

Although the antidepressant effects of ketamine are obvious from clinical trials, the underlying mechanism is still not clear. Ketamine is known to have variable clinical effects at different doses. For example, at higher doses it acts as a hypnotic anesthetic, lower doses may be hallucinogenic, and lower doses still appear to be antidepressant. This pattern is suggestive of variable affinities of different receptors or processes. For anesthesia, the presumed mechanism is its effects as a NMDA receptor antagonist [35]. However, this effect is unlikely to mediate the antidepressant effect since the drug has already been eliminated from the body at the height of clinical response. Dendritic spine density in multiple brain areas such as the prefrontal cortex, limbic system, and hippocampus is lower in animals susceptible to depression [36,37] and animals exposed to chronic stressor-a model for depression [38]. Similarly, the volume of the prefrontal cortex and hippocampus is reduced in patients with major depression [39,40]. Ketamine has been shown to rapidly (within 24 hours) increase the number of synapses in the prefrontal cortex [41,42]. These observations take into account pathophysiological changes seen in depression and the time course of those changes [43]. Furthermore, in animal models of depression, the R enantiomer of ketamine had a more potent antidepressant effect compared to S enantiomer [44,45]. That is despite that fact that S-ketamine 3-4 times more potent at inhibiting NMDA receptor compared to R-ketamine [46].

### Conclusion

Much is known about the pharmacological properties of ketamine owing to its long history of use as an anesthetic medication. Accumulating evidence suggests that it may also be a safe and effective antidepressant. Research looking at this and other glutamate system modulators is growing. However, while the antidepressant effect is rapid, it is relatively short-lived. Some studies have looked at repeated ketamine administration to obtain a longer lasting response [47] but there is a dearth of information on long-term effects of ketamine. Despite the promising initial results for the use of ketamine in treatment resistant depression, it is important to remember that it is still not approved by the FDA for that indication and still considered an experimental treatment. The American Psychiatric Association (APA) in 2017 released a consensus statement regarding the use of ketamine in depression [48]. In that document, the APA recommends caution as due to the huge gaps in knowledge that still exist. Clin-



ical researchers need to continue to examine the use of ketamine in treatment-resistant depression, with specific emphasis placed on the consequences of repeated dosing and long-term effects of both brief and extended exposure to ketamine.

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