

# Treating Depression Using Ketamine

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## Abstract

Unipolar major depressive disorder affects a significant number of individuals across the globe placing at the top of the list as the leading cause of disability, related to damaging ramifications on the well-being affected persons and the societies. The current standard antidepressants targeting monoamine systems take long in starting a response. Therefore, there is a need in depression patients that is yet to be satisfied efficacious and swiftly acting antidepressant like those containing ketamine agent. This paper attempts to proof why ketamine should be used to treat depression. It compares it with other agents like nitrous oxide and it evident that ketamine is much faster and more effective than current antidepressants.

**Keywords:** Ketamine; Depression; Antidepressant; Treatment; Drugs.

## 1. Introduction

Unipolar major depressive disorder impacts over 300 million individuals across the globe placing at the top of the list as the leading cause of disability, related to damaging ramifications on the well-being affected persons and the societies (Marcus and Yasamy, 2016). Today, existing anti-depressant targeting on monoamine system just relieves depressive manifestations in about 50 percent of patients (Papakostas and Ionescu, 2015). The rates become notably lower in individuals who were unable to respond or improve after anti-depressant therapeutics at sufficient doses (Undurraga and Baldessarini, 2016). This leads to unnecessary exposure to long experiments or studies or tests involving ineffective medications (Malhi and Byrow, 2016). In addition, the current standard antidepressants targeting monoamine systems take long in starting a response (normally 6-12 weeks). As a result, there is a need in depression patients that is yet to be satisfied efficacious and swiftly acting antidepressant like those containing ketamine agent.

Long utilized as an anesthetic and analgesic, large percentage of individuals who have come across it identify Ketamine for this purpose (Kirby, 2015). Another group recognize it as a party drug that enables consumers to have an out-of-body encounter where individuals are entirely detached from reality. However, little investigation about increase of off-label utilization in United States for depression, in most situations when other alternatives have been exhausted. Researchers are applauding this drug currently the most crucial new development in the field of psychiatry particularly due to its high success or effectiveness in treatment of major depression. Evidence obtained recently has displayed that apart from depression, ketamine has the potential to treat obsessive-compulsive disorders, PTSD (Feder *et al.*, 2019) and other treatment-refractory neuropsychiatric diseases.

Ketamine was confirmed United States FDA in 1970 like an anesthetic and much safer option to phencyclidine. Medical value and use of ketamine like an anti-depressant started being explored after some time due to stigma on ketamine's widespread recreational use in 1960s-1970s and ketamine at the beginning was just given intravenously.

## 2. Method and Results

In 2000, scientists were able to determine that Ketamine robust, fast-acting (efficient) and durable outcomes in depression. Through randomized, placebo-managed, crossover layout research, individuals diagnosed with depression were administered with 0.5 mg/kg of ketamine or saline during the initial day of trials. Treatment were changed after 7 days. Researchers determined that anti-depressant outcomes of ketamine started in 4 hours, climaxed at 72 hours and continued for 1-2 weeks afterwards (Kraus *et al.*, 2019).

In a 2006 research, the findings above were reproduced in an independent class of 18 patients suffering from depressive disease but had been resistant to standard medications. In comparison with patients that were given placebo, patients that were given ketamine displayed notable improvements in symptoms less than 110 minutes, of which 35 percent preserved notable response not less than 1 week (Zarate *et al.*, 2016).

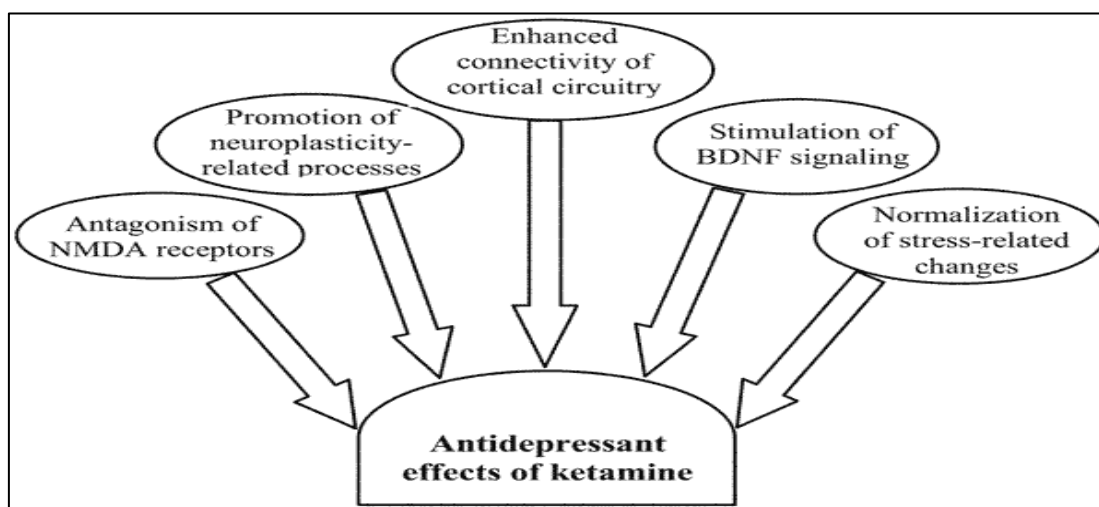
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### 3. Discussion

Various results from placebo-controlled researches have increasingly showed that this agent is enormously effective and durable in treating bipolar disease and other treatment immune depression disorders and brings about anti-suicidal and anti-anhedonia outcomes in mood disorders. A large number of current depression treatments tend to be monoaminergic-founded for example monoamine oxidase inhibitors and tricyclic antidepressants. Such treatments have proofed to be effective for most patients. But a notable number of subset patients suffering from major depression fail to respond to the agents (Nagele *et al.*, 2015). When set side by side with ketamine, the media contain held up start of action that at times remained so for some weeks. This raises the likelihood of organ failure and suicides.

One dose of ketamine is found to attain swift and strong outcomes just in hours-days of receiving it. It has also been found that ketamine quickly decreases suicidal thoughts, fatigue and anhedonia. This agent also enhances circadian rhythm as well as sleep models in depression. Scientists show that these signs are similar or closely related across various psychiatric diseases yet remain inadequately treated by monoaminergic-agents (Kraus *et al.*, 2019).

Notable distinctions between ketamine and common or ordinary antidepressants stimulated researchers to come up with new ketamine treatments; new ketamine therapeutics that are that are not that protruding like the treatments that include intravenous delivering or dispensation. In the third month of 2019, FDA accepted and confirmed an intranasal type of ketamine (esketamine) for mature patients suffering from treatment-resistant depression.



Researchers also point out that the agent's mechanism of action in clinical surroundings or settings, antidepressant effectiveness is just partly clear. At the moment, researchers only have knowledge and insight about this agent's mechanism of operation surpasses regulating neurotransmission of glutamate and it involves direct as well as indirect inflated attraction towards antagonistic binding effects. The binding effects occur at N-Methyl-D-aspartate receptor and as  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid all through regulation (Kraus *et al.*, 2019). Scientists have also been able to determine that this agent is not a strong agonist particularly at mu, delta, kappa opioid receptors. Additional systems which can be attributed to Ketamine's effectiveness when it comes to treatment of depression are like agonist at dopamine receptor, antagonism at M1-3 muscarinic receptors. Another contributor is prevention of re-uptake of serotonin. Scientist are keeping on with assessing ketamine's primary/fundamental mechanism of action to enable them go on with identifying and creating new agents that function in the same way but offer less side effects (Wan *et al.*, 2015) and longer treatment outcomes.

Ketamine has affected scientists to pay attention on glutamatergic systems when coming up with new therapeutics. This is because swiftly-acting ant-depressants may activate or start off biological incidents found in instant re-arrangement of limbic circuitries. Apart from esketamine, other swift-acting glutamatergic agents that display encouraging outcomes include nitrous oxide and sarcosine.

For about 150 years, nitrous oxide has played the role of an anesthetic and provides similar mechanism like ketamine. Findings from 2015 research show that patients suffering from treatment-resistant depressive disorder that were administered with nitrous oxide, had notable improvement in manifestations after 144 minutes in comparison to the placebo. Manifestations or signs that displayed much improved changes included depressed moods, guilt suicidal thoughts and anxiety (Nagele *et al.*, 2015). Extra tests and trials are being done to identify safety, effectiveness as well as optimum dosing of N<sub>2</sub>O for depressive disorder.

Sarcosine, being an amino acid, works like a glycine transmitter-1 inhibitor. It also contains co-agonistic effects at N-Methyl-D-aspartate receptor. Outcomes of the experiments display that these agent is an encouraging treatment of depression and has no negative effects. Nonetheless, when put side to side with ketamine, sarcosine fails to generate similar swift-acting outcomes and taking same duration. Researches are at the moment going on to reproduce effects of nitrous oxide and sarcosine in the depressive disorder.

It has been determined that Ketamine improves transmission of GABA to minimize depression. After accepting esketamine, FDA then accepted brexanolone agent which acts like a constructive allosteric regulator of gamma-aminobutyric acid receptors. At the moment, brexanolone is being utilized in treatment of postpartum depression. This is because this therapy brings about quick-and-durable antidepressant effects that are like those brought about

by ketamine. However, the exact mechanism of brexanolone is yet to be known and it still being experimented own as it has been associated to serious negative incidents like syncope, suicidal contemplation and overdosing.

Most studies having displayed the effectiveness of ketamine pertaining the depressive disorder, most scientists are reviewing or rethinking the promising gains of prohibited drugs for individuals in psychiatric complications. Psychiatric medicines being re-assessed are like psilocybin and LSD. Scientists are determining if micro-dosing these drugs would bring about therapeutic gains with no damaging side effects or overdose or drug use. Outcomes from the 2016 research show that psilocybin was fruitful at remarkably minimizing manifestations of the depressive disorder for as long as half a year in individuals received treatment for advanced cancer. In a research done in 2015 that aimed at looking at effects of lysergic acid diethylamide in individuals with severe ailments that were having uneasiness, LSD was found to be safe, can be tolerated and effective at minimizing psychiatric manifestations.

#### 4. Safety and Potential for Abuse

This agent has been determined to be safe as well as successful when used as an anesthetic in young ones and aged/mature individuals at doses 1-3 mg/kg (Wan *et al.*, 2015). If used for treatment of pain and depression ketamine can be given in doses 0.1-1mg/kg. The sub-anesthetic doses could be related to short-term neuropsychiatric effects like neurocognitive disturbances, dissociation, time-restricted elevation of heart rate and increase in blood pressure taking as long as 4 hours after receiving ketamine. Typical negative effects include dizziness, headaches, poor vision, vomiting, anxiety, and impaired coordination and so on Murrough *et al.* (2018). In the past ketamine was used for recreational purposes thereby making it highly probable for abuse and hence need for further research (DeWilde *et al.*, 2015). Because this drug is experimental, it is vital to appreciate and mind unstudied lifelong effects pertaining dosing and how often the doses are administered.

In summary, about one third of individuals suffering from depression have failed to respond to existing depressants and those patients that normally respond take longer time (weeks-months) to attain notable effect. The recent FDA acceptance of esketamine show a huge advance or development in psychiatry and progress in ketamine or ketamine-based therapeutics may largely enhance the quality of life of individuals diagnosed with the depressive disorder and have failed to respond to the current, standard treatments. Therefore, little research and modification is needed on ketamine to reduce side effects for it to be universally used to treat depression. The current standard antidepressants targeting monoamine systems take long in starting a response. Therefore, there is a need in depression patients that is yet to be satisfied efficacious and swiftly acting antidepressant like those containing ketamine agent. As discussed in the paper, ketamine is an efficient way of treating depression.

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