Review Article

Safety and Efficacy of Ketamine in Treatment-Resistant Depression (TRD)

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ABSTRACT

Depression is a widespread mental illness. About 264 million people worldwide are affected by depression at all ages. More women than men suffer from depression. Depression diagnosis includes at least two weeks of either low mood or anhedonism and 4 or more other symptoms such as shift of appetite or weight, insomnia or hypersomnia, psychomoting agitation, or delayed, lack of control, inability to focus, feelings of insignificance or excessive weight, according to Diastic and Statistical Manual, Fifth Edition (DSM-5). The treatment of moderate-serious depression can be a successful form of antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are the most widely used medications for depression, that target the monoaminergic system, but have some drawbacks, such as delayed initiation of action. The N-methyl d-aspartate receptor, or antagonist ketamine, was very interested in psychiatric studies, due to its rapid action against depression, in particular in patients who suffered from extreme treatment-resistant depression (TRD). The clinical effectiveness of ketamine in TRD has been addressed in this review with reliance on RCT data.

Keywords: Ketamine, depression, treatment-resistant depression (TRD).

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INTRODUCTION

Depression is one of the world's leading disability causes and a significant contributor to the global disease burden. A major depressive disorder (MDD) is a disabled disease which has frequent recurrences, incomplete recuperation between episodes and persistent psychosocial and functional disorder. MDD is considered one of the world's 10 leading causes of disability and is also linked to an increased risk of suicidal conduct. Nearly 8, 00, 000 people die every year as a result of suicide[1]. In the 15-29-year-old, suicide is the second most important cause of death. While numerous psychoactive agents for MDD are available at present, about 10-20% of patients treated with common antidepressant medicines have not been completely recovered and meet the therapeutic resistance criteria[2].

Treatment-resistant depression (TRD) affects more than 1% of people in the United States and may be classified as refractory in around 30% of all patients with depression. TRD is a psycho-social impairment-related disorder and with poor social-occupational results. While the present literature provides many definitions of TRD, TRD can generally be defined as a failure of at least two types of antidepressants to respond to the maximum dose for a period greater than 4 weeks. The pathogenesis of TRD remains very ambiguous to date[3].

Depression symptoms are largely due to a synaptic deficiency in monoamine supply according to monoamine hypothesis, and most antidepressant pharmaceutical products (e.g., norepinephrine, dopamine or serotonin) are assumed to modulate these monoamine neurotransmitter systems. Since it is well known that after 4 to 12 weeks of treatment only emerges the therapeutic effect with the traditional antidepressant drugs, pharmacological agents which produce rapid antidepressant effects may also be considered an unmet need for clinical practice. It is essential that clinicians concentrate on new molecular objectives beyond the monoamine paradigm to create more efficient drugs[4].

In many normal and abnormal physiological processes, glutamate, the most important amino acid of the central nervous system, plays an important role. Glutamate systems have been directly or indirectly involved in mood and anxiety[5], schizophrenia, alcohol abuse, and various neurodegenerative disorders (such as strokes and other traumatic brain injury, Alzheimer's disease, ALS).

Glutamate receptors are divided into the two main classes "ionotrope" and "metabotropic" and are dividable into 3 groups: N-methyl - D-aspartate, alpha amino-3-hydroxy-5-methyl-4-isoxaproprionic acid and kainate. There are also several subtypes of each category. Although there is interest in AMPA and metabotropic receptors, most relevant clinically relevant studies focus on medicines modulating glutamate function via NMDA receptors. More than 50 years ago, it was reported that the first glutamate-modulating drug therapy was used. Cycloserine is an antibiotic medication that was initially formulated to treat

TB. When administered at high-dose levels to depressed tuberculosis patients, Crane reported cycloserine with substantial antidepressant effects in 1959 but also with extreme neuropsychiatric adverse reactions[6].

Ketamine is a high-affinity non-competitive receptor aspartate (NMDA), but can bind to opioid μ and sigma receptors at higher doses. This medication interferes with the glutamate neurotransmitter (brain chemical)[7]. Glutamate involves with recognising, memory, emotion, perception of pain. It can be helpful to contribute to a fast heart rate and high blood pressure.

This agent is a lipid soluble compound with an initial fast distribution and a large volume of distribution, and 10 to 15 minutes of half-life period[8]. The drug is distributed in peripheral tissue, with slower removal half-life up to 3 hours, through hepatic metabolism and urine excrete[9].

Ketamine have been associated in animal depression models with antidepressant effects and in human depression studies with fast antidepressant effects[10].

It can help to alleviate pain at lower doses. Ketamine may help sedatives function and encourage patients to use less addictive painkillers, such as morphine during surgery[11].

Abuse of large doses can also lead to intense, environmental stimulus visual hallucinations. There could be coma and extreme inconscience, and it is exploited as a date-rape drug. In the case of abuse of more ketamine or during emergence, it is stated to be a vibrant dream and to create a hallucinogenic "out of body," "K hole" or "near death." Long-term consumption risks can be fatal[12].

Yet ketamine is a safe and effective drug, if correctly administered by a qualified medical professional.

REVIEW

1. In March 2019, esketamine, ketamine-based nasal spray, has been approved for depression by the Food and Drug Administration (FDA). Studies showed that small doses of ketamine can rapidly ease depression symptoms. Even individuals who have not reported beneficial effects in hours from other antidepressants[13]. The willingness of Ketamine to function for these hard-to-treat people could be attributed to his new way of behaving. The drug blocks the N-methyl - D (NMDA) receptor of glutamathergic substances; other antidepressants interact with serotonin, norepinephrine, or adrenaline. Owing to very little improvement in recent years in depression care, ketamine has caused optimism and renewed hope. Scientists also raised fears about the side effect of ketamine, including feelings of dissociation, rise in blood pressure, respiratory distress, vomiting, and cystitis alongside this favour . The primary objective of this study was to extensively investigate [side-effects] related to ketamine by analysing 120 symptoms linked to one infusion of subanesthetic ketamine[14].

In order to analyse the results, 163 people with major depressive or bipolar disorders and 25 healthy controls were identified in studies conducted by NIH over the past 13 years. Due to its thorough tracking of side effects at various stages, including uniform rating scales and clinician interviews, the researchers chose NIH studies. The researchers could associate 33 with ketamine treatment overall, of the 120 symptoms. Eight of these symptoms were seen in more than half of the participants; they felt strange, peculiar, or bizarre; they felt spatial. They felt woozy or loopy; they were dissociated, they had floating. None of these results, however, lasted for 4 hours. The investigators did not detect significant adverse effects, such as cravings, memory disorders, and cognitive impairment during a 3-month follow-up session. The authors also state that "no rise in the sensitivity to recreational ketamine or assault" has been demonstrated[15].

"The most prevalent side effect in the short term was to feel confused or loopy. Most adverse events occurred within an hour and were gone within 2 hours. We did not see any significant adverse drug-related events or increased ketamine cravings with one dose[16].

2. Researchers found in 2000 that ketamine caused strong, rapid, and long-term depression effects. Patients with a depression received 0.5 mg / kg ketamine or saline on the first day of a randomised, placebo-controlled crossover design trial. One week later, treatments have been changed. In a 2006 study, this finding was replicated in an autonomous group of 18 patients with major depressive disease resistant to other therapies, and the antidepressants effects of ketamine were reproduced within 4 hours and peaked at 72 hours. Compared with placebo-positive participants, symptoms of ketamine improved substantially within 110 minutes, with 35% maintaining a vital response for at least 1 week[17].

3. In 2016, Jaclyn Schwartz et al. carried out a review on Ketamine for therapy-resistant depression: recent advances and clinical applications, addressing the efficacy of ketamine, of which the majority of neuropsychiatric and neurocognitive illness are long lasting; however, the long-term effects of ketamine remain uncertain. Suicidal ideation (SI) is among the most clinically concerning of depression, and remains a leading cause of death. The majority of research examining ketamine effectiveness for depression removed people at the imminent risk of suicide but also included patients with moderate degree of SI. Studies are consistent with a substantial reduction in SI following administration of ketamine. They are eventually concluded with essential ketamine data for primary and secondary doctors as evidence for probable use in the clinical environment begins to appear, indicating the need for further study of their results[18].

4. In 2014, Gianluca Serafini et al. performed the Role of ketamine in Treatment- Resistant Depression: A Systematic Analysis, at least 10–20%of depressed patients fulfil requirements for TRD. The role of glutamate in mood control has been hypothesised over last few decades and ketamine has proved its effectiveness in both the MDD and

TRD in the non-competitive antagonist of the N-methyl - D-aspartate (NMDA) receptors. Nevertheless, there have been questions about the appropriate dose and the duration of this procedure. Most studies show the quick antidepressant effects of NMDA antagonist ketamine in TRD patients, supporting the active function of glutamate in this complex condition's pathophysiology. The effectiveness of ketamine was shown to be swift and a clinical improvement in depressive symptoms was demonstrated within hours of treatment. Ketamine also has been found to be effective in reducing TRD suicide. They have concluded that ketamine could be a viable and interesting alternative in treating TRD. Further studies are required to determine the long-term efficacy of its antidepressant in TRD patients[19].

5. In 2019, a review on Clinical Efficacy of Ketamine for Treatment-resistant Depression was conducted by Sosipatros Bratsos et al., According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the diagnosis of depression requires at least two weeks of either low mood or anhedonia as well as four or more other symptoms such as appetite or weight changes, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, inability to concentrate, feelings of worthlessness or excessive guilt, and suicidality. Recent evidence involves a glycolamatergic system in depression pathogenesis, which has generated enormous interest. Agents which aim to modify this system. Ketamine, the noncompetitive antagonist of NMDA receptors, was particularly highlighted by its rapid antidepressant effects, especially in patients who are considerably less likely to respond to another antidepressant and have a higher risk of functional disability, with a high level of resistance to therapeutic depression (TRD). This review aims to discuss the clinical efficacy of ketamine for TRD by evaluating the available evidence and specially randomised controlled trials, which evaluated the impact of ketamine in patients with TRD. In summary, the use of ketamine in kED has demonstrated promise, yet problems in its applications. TRD refers to depression that does not respond to more than two antidepressants[20].

DISCUSSION

Ketamine was found to have a rapid and continuous antidepressant effect on samples of TRD patients based on the majority of included studies. All randomised studies in our review suggested that ketamine is a promising and innovative pharmacologic option, contrasting to the delayed treatment of current antidepressant medicines which take several Weeks before acting, for the active and rapid antidepressant properties of the drug in TRD.

Based on its benefits as a fast start-up of action, ketamine can be considered a viable choice for TRD. In the study conducted by Jaclyn Schwartz et al., the safety of ketamine has been discussed, which has a short-lasting of neuropsychiatrical, neurocognitive and cardiovascular disorder. They also concluded that ketamine remains evidence for its possible use in clinical settings for primary and secondary physicians and emphasises the need to examine its effects further.

Gianluca Serafini et al. performed a systematic study, with at least 10-20% of depression-resistant (TRD) patients meeting requirements.

The TRD Clinical Efficacy Analysis by Sosipatros Bratsos et al. Showed that ketamine was promising, however, issues related to its applicability in clinical practise as well as its long-term consequences should be tackled in future.

Esketamine — a ketamine-based nasal spray — has been approved for depression by the Food and Drug Administration (FDA) in March 2019. They concluded that it was unusual or loopy to experience the most popular short-term side effect. Most of the side effects occurred in an hour's time and were gone within 2 hours of administration. We have seen no severe, therapeutic side effects or increased cravings with ketamine in one administration.

Researchers also found in 2000 that ketamine had solid, rapid and long-term depression effects. Compared with placebo-positive subjects, symptoms of ketamine improved significantly within 110 minutes, with 35% sustaining an effective response for at least 1 week.

CONCLUSION

The safety and effectiveness of ketamine was assessed in this analysis for the treatment of TRD patients. It has been shown that ketamine causes quick antidepressant effects in patients with TRD up to a week after an intravenous infusion, whereas the effect has lasted up to 15 days twice or thrice weekly. However, ketamines in their infancy are still in a clinical trial for ketamines in depression and more long-term RCTs with good active control are still needed in order to accurate evaluation of their effectiveness. Future studies are required to try to improve strategies for preserving the long-term rapid reaction of antidepressant ketamine.

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