Proceedings of 3rd International Conference on Interdisciplinary Humanities and Communication Studies
DOI: 10.54254/2753-7064/40/20242334

The Effectiveness of Ketamine Treatment on Depression

Yichen Liu[1,a,*]

[1]*Shanghai Pinghe Bilingual School, Shanghai, China*
a. liuyichen@shphschool.com
**corresponding author*

Abstract: As the diagnosis rate of depression continues to rise, effective treatment options for this condition have become one of the most researched areas in the field. Earlier antidepressants were primarily developed based on mechanisms that involve regulating imbalanced neurotransmitters. For example, the widely known Selective Serotonin Reuptake Inhibitors (SSRIs) and various tricyclic antidepressants work by adjusting the concentration of different neurotransmitters, such as dopamine and norepinephrine, in the synaptic cleft to alleviate depressive symptoms. Additionally, many therapeutic approaches have been developed and applied based on the widely accepted hormone hypothesis and neurotrophic factor hypothesis. Ketamine, a drug traditionally used as an anesthetic, has recently been discovered to possess antidepressant properties. Its efficacy and underlying neuroscientific mechanisms are currently under investigation. Unlike earlier antidepressants, Ketamine produces significant antidepressant effects within a short time after administration. Multiple studies have suggested that Ketamine's rapid and effective therapeutic results may be based on entirely new antidepressant mechanisms and targets that have yet to be fully understood. This provides a new solution for the treatment of treatment-resistant depression and offers new hope to patients who have tried various treatments without success. In this literature review, Ketamine's therapeutic effects and its underlying mechanisms will be thoroughly examined. The content will be divided into three sections: significant antidepressant effects, underlying principles and mechanisms, and factors relevant to the improvement of Ketamine therapy.

Keywords: depression, Ketamine, treatment resistance.

1. Introduction

Depression is a common mental health disorder that can lead to significant personal distress and impairment of social functioning, with symptoms typically lasting for at least two weeks for each episode. The primary symptoms of depression include persistent negative emotions, sleep disturbances, changes in appetite, difficulty concentrating, and social interaction issues. These symptoms can affect all aspects of a person's life, including mental and physical health and social behavior. In severe cases, if left untreated, individuals may develop thoughts of suicide or suicidal attempts. According to the World Health Organization, more than 280 million people worldwide are affected by depression, accounting for 3.8% of the global population (WHO, 2023). It is estimated that by 2030, depression could become the second leading cause of disease burden globally. These statistics indicate that depression has become one of the most prevalent mental health disorders.

DOI: 10.54254/2753-7064/40/20242334

Currently, the monoamine hypothesis remains one of the most widely accepted explanations for the pathophysiology of depression. This hypothesis suggests that dysfunction in monoamine neurotransmitters, such as dopamine, serotonin, and norepinephrine, is a primary cause of depressive symptoms. In a depressive state, the concentration of these monoamines in the synaptic cleft is reduced [1]. Many commonly used antidepressants are based on the monoamine hypothesis. For example, early tricyclic antidepressants like imipramine work by inhibiting the reuptake of serotonin and norepinephrine in the synaptic cleft, thereby increasing the concentration of these neurotransmitters. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, also operate on this principle [2]. In addition to the monoamine hypothesis, the overactivation of the hypothalamic-pituitary-adrenal (HPA) axis and the associated stress response is another major factor in the onset of depression. Under normal circumstances, the release of glucocorticoids following HPA axis activation helps enhance hippocampal function. However, in cases of chronic severe stress, sustained high levels of glucocorticoids can exert neurotoxic effects and damage hippocampal neurons, impairing important cognitive functions. Chronic stress can also reduce the levels of brain-derived neurotrophic factor (BDNF) in the hippocampus, negatively affecting neurogenesis (the formation of new neurons) and neural plasticity [3]. Furthermore, recent studies have shown that glutamate ion channel-dependent burst firing in the lateral habenula is a significant cause of anhedonia and behavioral despair. The frequent firing of the lateral habenula enhances the inhibition of dopaminergic neurons, preventing individuals from experiencing pleasure [4].

Although the current common antidepressants can relieve depression in most patients with mild symptoms, there are still exceptions. Treatment Resistance Depression (TRD) usually refers to insufficient response to at least one adequate dose and course of antidepressant trial. Up to 10%-20% of patients with depression are suffering from TRD [5]. In recent years, research on the treatment of TRD has been increasing, and Ketamine, an emerging drug, has performed well in it. Ketamine is a fast-acting antidepressant that was originally developed as an anesthetic, it is unique compared to traditional antidepressants, such as SSRIs and TCAs, in that it eases depressive symptoms within hours rather than weeks. Most patients who have not responded to monoamine antidepressants have made considerable progress after receiving Ketamine therapy. This not only support that the antidepressant effect of Ketamine comes from a new mechanism, but also brings new hope for the treatment of refractory depression. Due to ketamine's significant efficacy and achievements in treating depression, this paper will explore the drug in depth. The discussion will cover its positive therapeutic effects on depression, the underlying neural mechanisms, and factors that could further enhance its effectiveness.

2. The Positive Impact of Ketamine on Depression

2.1. Overall Effectiveness of Ketamine on Depression

Since Ketamine emerged as a novel antidepressant in the treatment of depression, numerous studies and trials have been conducted to evaluate its efficacy. The majority of these studies have demonstrated that Ketamine is indeed effective in treating depression. Mandal and colleagues evaluated the efficacy of Ketamine treatment on depression in 2019. There are 25 drug-free male participants who are diagnosed with depression involved in this experiment. The baseline assessment (i.e., Hamilton Depression Scale, a standard scale for depression diagnosed) is given before they receive any treatment. Their scores are all above 16 which suggests that their depression is severe. After that, they received six Ketamine administrations within 2 weeks, the researcher let them do the assessment one hour after the administration every time. After the final administration, they did the last assessment. Their scores suggest that after 2 weeks Ketamine therapy, their symptoms diminish and relieve a lot. This effect sustained for at least one month [6]. Not only has this research confirmed

DOI: 10.54254/2753-7064/40/20242334

Ketamine's significant impact on alleviating depressive symptoms, but it also highlighted the lasting effects of the treatment, which continue for a considerable period after the treatment ends. This is particularly beneficial for patients who require long-term therapy. Moreover, all participants in the study had not taken any form of medication or received any treatment prior to the experiment, ensuring that the therapeutic effects observed were solely due to Ketamine, free from any confounding effects of other treatments.

What truly sets Ketamine apart and has made it one of the most anticipated new antidepressants is its effectiveness in treating not only typical depression but also treatment-resistant depression (i.e., patients with major depressive disorder who had not responded to at least two adequate trials of antidepressants are diagnosed with the TRD). In the study by Phillips and colleagues, they investigated the efficacy of Ketamine for patients with TRD who experience suicidal ideation by using a randomized, double-blind, placebo-controlled design. The suicidal ideation was measured by Montgomery–Åsberg Depression Rating Scale (i.e., a clinically used depression scale with good sensitivity to changes during treatment of depression) and the Quick Inventory of Depressive Symptomatology Self-Report 16-item version. (The score ranges from 0 to 27, with higher scores indicating more severe depression). Participants (i.e., individuals with TRD and have active suicidal ideation) will either receive multiple Ketamine infusions or placebo infusions, administered thrice weekly over 2 weeks. Those who developed an antidepressant response also received an additional four weeks of weekly injections. After treatment, their suicidal ideation was measured in several time points to test both the immediate and sustained effects. As a result, Ketamine showed rapid reduction in suicidal ideation compared to placebo with significant improvements noted as early as 24 hours post-infusion [7]. Overall, 69 percent of participants experienced complete remission of SI after repeated infusions (i.e., shown by the comparison between the baseline scores and the after treatment scores of two standard scales). This suggests that it is effective to use Ketamine as a short term treatment for those patients who are diagnosed with TRD. The rapid onset of Ketamine's effects is crucial for patients with severe depression who are at constant risk of suicide. Unlike traditional antidepressants, such as SSRIs, which require a gradual and prolonged treatment period to become effective, Ketamine offers immediate relief, swiftly eliminating suicidal thoughts. This immediacy makes Ketamine an irreplaceable option in antidepressant therapy.

Furthermore, Ketamine stands out even when compared to other common treatments for treatment-resistant depression. Mathew and colleagues compared the efficiency of the Ketamine treatment and the Electroconvulsive therapy (ECT) (i.e., Stimulating the brain with a brief electrical current, regulating brain chemicals and alleviating severe depressive symptoms) on depression by using an open label, randomized, noninferiority trial conducted across five clinical centers. The purpose of such trials is to determine whether a new treatment is at least as good as existing standard treatment, in this case, the Electroconvulsive therapy. In the experiment, participants received either Ketamine administration or Electroconvulsive therapy within three weeks. The result shows that the Response rates (i.e., QIDS-SR-16)) score decreased by 55.4% for Ketamine and 41.2% for ECT after 3 weeks treatment, suggesting that the Ketamine treatment is noninferior than the ECT [8]. At the same time, Ketamine administration shows relatively mild side effects (e.g. disassociation), which diminished within a short time period. This study show that its efficacy is comparable to traditional methods like ECT, while its side effects are significantly milder and less distressing for patients. In short, Ketamine has consistently proven its remarkable therapeutic benefits in numerous studies. Its rapid action and minimal side effects have distinguished it as one of the most promising and eagerly awaited antidepressants available.

DOI: 10.54254/2753-7064/40/20242334

2.2. Neural Mechanism Underlying the Effectiveness of Ketamine

To investigate why Ketamine is so effective and works so quickly, scientists have conducted numerous experiments in recent years to explore its unique mechanisms. The study carried out by Fuchikami et al. investigated how activating specific neurons in the infralimbic prefrontal cortex (IL-PFC) can mimic the rapid and long-lasting antidepressant effects of Ketamine. In the experiment, researchers used the Optogenetic Activation (i.e., using light-sensitive proteins to control neuronal activity with light.)to specifically activate the target neurons in some rodents (Adult male Sprague-Dawley rats (from Charles River Laboratory), weighing 150-250 g, were kept in pairs during a 12-hour light/dark cycle (with lights on at 07:00) with free access to food and water. All indicators are normal). The result shows that the activation can promote significant antidepressant and anxiolytic behaviors (i.e., antianxiety) in rodents [9]. After comparison, they found that the effect of the activation is very similar to what is observed after the Ketamine administration (i.e., rapid and sustained antidepressant effects), suggesting that the antidepressant mechanism of the Ketamine treatment could be the modulation of neuronal activity in the IL-PFC. Although the researchers reached this conclusion, the experiment provided no direct evidence linking IL-PEC and Ketamine's mechanism of action. The observed similarity was merely noted, without establishing a substantial connection.

However, another experiment identified changes in specific brain region activity following Ketamine injection, pinpointing one of the potential targets of Ketamine's mechanism of treatment. Yang et al. investigated how Ketamine exerts its rapid antidepressant effects. The primary focus of the research is on the lateral habenula (LHb), a brain region implicated in depression. The researcher first found that the activation of neurons in the lateral habenula by optogenetic technique led to significantly depressive-like behaviors in animal models (i.e., despair and anhedonia). Increased burst activity and theta-band synchronization in LHb neurons are also observed in those depressive-like animals. This suggests that the activity of LHb is highly related to depression. After that, they administered Ketamine specifically into the LHb of some animals who present depressive behaviors. The data of the Electrophysiological Recordings shows that Ketamine rapidly reverses the increased burst activity in the LHb [4]. With this result, the researchers proposed a model that Ketamine's inhibition of NMDAR-dependent can burst in the LHb, disinhibits midbrain dopaminergic and serotoninergic neurons, which are crucial for activating brain reward centers in order to reach the antidepressant effects. This study was not only found that Ketamine's rapid and effective antidepressant effects are related to its role as an NMDA receptor antagonist, but also was the first paper to demonstrate the interaction between Ketamine and the anti-reward center, the LHb. The result brings significant advancements to the research on Ketamine's antidepressant mechanisms, which had previously been largely speculative.

Additionally, potential mechanisms explaining Ketamine's relatively long-lasting antidepressant effects have also been explored. The study carried out by R. N. Moda-Sava and colleagues investigated how antidepressants, particularly Ketamine, induce dendritic spine (i.e., important sites of synaptic transmission in neurons, acting as the key factors in nerve signal transmission and neuroplasticity) formation in the medial prefrontal cortex (mPFC) to alleviate depression. By using the longitudinal imaging and the animal model, the researcher found out that Depression-related behavior in mice is associated with the elimination of dendritic spines in the mPFC. The administration of Ketamine can partly repaired these dendritic spines loss and promote related multicellular ensemble activity in neurons projected to the PFC. The immediate effects of Ketamine on those neural activities are the reason why the treatment can rapidly reverse the depressed symptoms. At the same time, the spinogenesis (i.e., the new formation of dendritic spines) is very essential for the long-term maintenance [10]. Before Ketamine was used as an antidepressant, the

DOI: 10.54254/2753-7064/40/20242334

dendritic spines damaged by depression could not be repaired, leading to prolonged negative impacts on corresponding neural activity. Ketamine's promotion of spinogenesis suggests that the neural damage caused by depression can be reversed, with the newly formed dendritic spines being maintained over the long term. This lasting effect is something other medications cannot achieve.

Despite these significant advances in understanding Ketamine's mechanisms, all these studies share a common limitation: they were conducted on animal models. Currently, there are very few human studies exploring Ketamine's mechanisms. Therefore, although the neural mechanisms observed in animals are somewhat similar to those in humans, more human studies will likely be needed in the future to further support Ketamine's actual mechanism of action.

3. Factors Relevant to the Improvement of Ketamine Therapy

Although numerous studies have confirmed that Ketamine is highly effective in treating depression, the method of administration and dosage can significantly influence its efficacy. To optimize treatment, scientists have conducted various experiments. In the study by Loo et al., the efficacy and safety of repeated subcutaneous Ketamine injections in patients with TRD was assessed using randomized, double-blind experiment. There are two cohorts involved in this experiment, fixed-dose cohort and flexible-dose cohort (i.e., whether the amount of medicine can be adjusted based on the situation). Ketamine or midazolam (placebo) were injected subcutaneously twice a week for 4 weeks. The data was collected 3-4 days after the final treatment. The result shows that in the flexible-dose cohort, patients that are treat with Ketamine have a higher remission rate (i.e., measure by the Montgomery–Åsberg Depression Rating Scale) [11]. The side effects of Ketamine can be resolved within two hours of administration , which also suggests that Ketamine is safe and well-tolerated. This experiment showed that when a fixed-dose injection method was used, the effects of Ketamine were almost identical to those of a placebo. This finding suggests that for Ketamine therapy to be effective, patients must receive a dosage tailored to their individual condition to ensure the best therapeutic outcome.

Another study indicated that, in addition to using Ketamine after depressive symptoms appear, administering Ketamine preemptively could effectively prevent a range of depressive symptoms triggered by anxiety. A study carried out by Rebecca et al. investigated the effect of Prophylactic administration (i.e., the use of a treatment or intervention to prevent the onset of a disease or condition before it occurs) of Ketamine on some Stress-Induced Depressive-Like Behavior by using animal model. Some wild type mice received the administration of either Ketamine or saline water (placebo). After one week, they were all put into some stress model and their behaviors were observed. The study used various stress models to simulate psychiatric conditions, such as SD (i.e., exerting stress by letting those mice experience social failure), forced swim test and the dominant interaction test. The result shows that a single low-dose injection of Ketamine can protect against stress-induced depressive behavior in mice [12]. This is effective for at least four weeks. This suggests the potential for using Ketamine as a preventive treatment for stress-related psychiatric disorders in humans. While the experiment demonstrated the feasibility of this approach, preventive Ketamine injections have not yet been widely adopted. More studies need to be carried out to validate this method and facilitate its clinical application. Another feature of Ketamine is that it has high response and remission rates, and it only takes 4 to 72 hours to produce an effect for one dose [13]. One of the major drawbacks of other monoamine drugs or tricyclic drugs is that they take a very long time to take effect. The most common SSRI takes about two weeks to take effect, during which time the patient's existing anxiety and suicidal thoughts are likely to intensify [14]. Therefore, the fast onset of Ketamine is very unique and important.

DOI: 10.54254/2753-7064/40/20242334

4. Conclusion

Numerous studies have demonstrated that Ketamine is a fast-acting and effective novel antidepressant. Its efficacy extends beyond common forms of depression to treatment-resistant depression, where it has shown positive results even when other treatments have failed. Compared to traditional methods used to treat treatment-resistant depression, Ketamine is well-tolerated, with relatively mild side effects that usually subside shortly after discontinuation. According to multiple studies, Ketamine's antidepressant mechanism may be linked to its role as an NMDA receptor antagonist. By inhibiting NMDA receptor-mediated neurotransmission, Ketamine reduces burst firing in the LHb, thereby mitigating the LHb's negative regulatory effect on emotion and reward processing. Additionally, Ketamine's ability to promote dendritic spine regeneration in certain brain regions contributes to its longer-lasting antidepressant effects. It is worth noting that both of the potential antidepressant mechanisms of ketamine mentioned above were discovered in animal model experiments. Whether these mechanisms can be fully applied to humans remains to be determined.

As previously mentioned, most studies on the antidepressant mechanisms of Ketamine have been carried out using animal models. While this approach holds significant value in scientific research, it also comes with several limitations. Firstly, there are considerable interspecies differences between animals and humans, such as in physiology, genetics, and metabolism. Even though some physiological functions may be similar between animals and humans, the resulting physiological responses can differ significantly. This disparity can lead to differences in how experimental results translate from animals to humans. Moreover, humans have complex behaviors and physiological processes influenced by social, cultural, educational, and emotional factors. These factors are difficult to replicate in animal models. This is especially true for mental disorders like depression, where emotions and external social factors play a substantial role in the onset and progression of the disease. Therefore, results derived from animal models may not fully reflect real-world situations. Secondly, the environment in which animal model experiments are conducted is artificial and differs significantly from the natural environments in which humans live. The laboratory conditions may cause animals to exhibit behaviors that do not align with their natural state, potentially affecting the final experimental outcomes. Thus, more research based on human subjects should be carried out to avoid these potential limitations and increase the likelihood that experimental theories can be applied in real life.

Although significant progress has been made in research on the antidepressant effects of Ketamine, there are still many areas that require further exploration and development. Studies have shown that there are very few experiments investigating the long-term safety of Ketamine use. While Ketamine has shown excellent short-term efficacy, people still need to consider whether long-term use could lead to drug tolerance, increased side effects, or adverse effects on cognitive function and physical health. Additionally, Ketamine's effectiveness may vary among individuals, so future research could focus on developing personalized treatment plans. For example, genetic testing or neuroimaging techniques could be used to predict which patients are most likely to respond positively to Ketamine treatment, thereby optimizing dosage and treatment protocols. Some patients may not be well-suited to the most common method of Ketamine administration, intravenous injection, so exploring more varied and convenient delivery methods is also a potential future research direction.

References

[1] *Boku, S., Nakagawa, S., Toda, H. and Hishimoto, A. (2017). Neural basis of major depressive disorder: Beyond monoamine hypothesis. Psychiatry and Clinical Neurosciences, 72(1), 3–12.*

[2] *Hirschfeld, R.M. (2000). History and evolution of the monoamine hypothesis of depression. Journal of clinical psychiatry, 61(6), 4-6.*

DOI: 10.54254/2753-7064/40/20242334

[3] *Nestler, E.J., Barrot, M., DiLeone, R.J., Eisch, A.J., Gold, S.J. and Monteggia, L.M. (2002). Neurobiology of depression. Neuron, 34(1), 13-25.*

[4] *Yang, Y., Cui, Y., Sang, K., Dong, Y., Ni, Z., Ma, S. and Hu, H. (2018). Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. Nature, 554(7692), 317-322.*

[5] *Serafini, G., Howland, R., Rovedi, F., Girardi, P. and Amore, M. (2014). The role of Ketamine in treatment-resistant depression: a systematic review. Current neuropharmacology, 12(5), 444-461.*

[6] *Mandal, S., Sinha, V.K. and Goyal, N. (2019). Efficacy of Ketamine therapy in the treatment of depression. Indian journal of psychiatry, 61(5), 480-485.*

[7] *Phillips, J.L., Norris, S., Talbot, J., Hatchard, T., Ortiz, A., Birmingham, M. and Blier, P. (2020). Single and repeated Ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. Neuropsychopharmacology, 45(4), 606-612.*

[8] *Anand, A., Mathew, S.J., Sanacora, G., Murrough, J.W., Goes, F.S., Altinay, M. and Hu, B. (2023). Ketamine versus ECT for nonpsychotic treatment-resistant major depression. New England Journal of Medicine, 388(25), 2315-2325.*

[9] *Fuchikami, M., Thomas, A., Liu, R., Wohleb, E.S., Land, B.B., DiLeone, R.J. and Duman, R.S. (2015). Optogenetic stimulation of infralimbic PFC reproduces Ketamine's rapid and sustained antidepressant actions. Proceedings of the National Academy of Sciences, 112(26), 8106-8111.*

[10] *Moda-Sava, R.N., Murdock, M.H., Parekh, P.K., Fetcho, R.N., Huang, B.S., Huynh, T.N. and Liston, C. (2019). Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. Science, 364(6436), eaat8078.*

[11] *Loo, C., Glozier, N., Barton, D., Baune, B.T., Mills, N.T., Fitzgerald, P. and Rodgers, A. (2023). Efficacy and safety of a 4-week course of repeated subcutaneous Ketamine injections for treatment-resistant depression (KADS study): randomised double-blind active-controlled trial. The British Journal of Psychiatry, 223(6), 533-541.*

[12] *Brachman, R.A., McGowan, J.C., Perusini, J.N., Lim, S.C., Pham, T.H., Faye, C. and Denny, C.A. (2016). Ketamine as a prophylactic against stress-induced depressive-like behavior. Biological psychiatry, 79(9), 776-786.*

[13] *Katalinic, N., Lai, R., Somogyi, A., Mitchell, P.B., Glue, P. and Loo, C.K. (2013). Ketamine as a new treatment for depression: a review of its efficacy and adverse effects. Australian & New Zealand Journal of Psychiatry, 47(8), 710-727.*

[14] *Bratsos, S. and Saleh, S.N. (2019). Clinical efficacy of Ketamine for treatment-resistant depression. Cureus, 11(7).*