ISSN: 3068-1790
Research Article
Annals of Rehabilitation and Regenerative Medicine

The Neuroregenerative Potential of Ketamine in Depression: Pathways to Cognitive and Emotional Rehabilitation

Lubna Al-Gailani*, Sevda Lafci Fahrioğlu, & Ali Al-Kaleel

Faculty of Medicine, Cyprus International University, Nicosia, Cyprus

***Corresponding author:** Lubna Al-Gailani, Faculty of Medicine, Cyprus International University, Nicosia, Cyprus

Submitted: 01 October 2024 **Accepted:** 07 October 2024 **Published:** 11 October 2024

https://doi.org/10.63620/MKARRM.2024.1002

Citation: *Al-gailani, L., Fahrioğlu, S. L., & Al-kaleel, A. (2024). The neuroregenerative potential of ketamine in depression: Pathways to cognitive and emotional rehabilitation. Ann of Rehabil & Regene Med 1(1), 01-06.*

Abstract

Depression, a leading cause of disability worldwide, presents significant challenges in treatment due to delayed therapeutic effects and incomplete remission in many patients. Recent advances have explored the potential of ketamine an NMDA receptor antagonist, in treating depression beyond its role as an anesthetic. Emerging evidence suggests ketamine has unique neuroregenerative properties, promoting synaptogenesis, neuroplasticity, and neural repair in key brain regions such as the hippocampus and prefrontal cortex. This review explores the neuroregenerative mechanism of ketamine, emphasizing its role in cognitive and emotional rehabilitation in patients with treatment-resistant depression (TRD). Preclinical and clinical studies demonstrate ketamine's rapid antidepressant effects, which are thought to result from enhanced synaptic plasticity and increased dendritic spine density. The ability of ketamine to alleviate depressive symptoms quickly, coupled with its potential to repair cognitive dysfunction, makes it a promising therapeutic candidate.

Additionally, ketamine's role in regulating glutamatergic transmission, preventing synaptic damage, and supporting emotional and cognitive recovery offers a novel approach to treating major depressive disorder. Further research is needed to fully reveal ketamine's long-term effects, optimal dosing strategies, and its potential in combination with other therapeutic modalities. This paper highlights the need for continued investigation into the neurobiological mechanism underlying ketamine's antidepressant effect and its application in clinical practice.

Keywords: Depression, Ketamine, Neuroplasticity, Synaptogenesis, Treatment-Resistant Depression

Introduction

In literature, there are previous studies that have examined the effectiveness of ketamine, an N-methyl D-aspartate (NMDA) receptor antagonist, through various administration methods, including intravenous (IV), intranasal (IN), and oral routes [1]. Research has also explored the efficacy and safety of different ketamine formulations, such as racemic ketamine, and the enantiomers esketamine and arketamine [2-4]. For treatment-resistant depression (TRD), IV racemic ketamine and IN esketamine deliver rapid antidepressant and anti-suicidal effects within 24 hours of administration [5-7]. The fast-acting efficacy of IV ketamine in TRD patients has been further validated by numerous randomized, double-blind, placebo-controlled trials, as well as large case series from clinics offering off-label, repeat-dose ketamine treatments for unipolar and bipolar TRD.

Emerging evidence in preclinical and clinical studies suggests that ketamine can do significantly more than aid in alleviating depressive symptoms [8]. The discovery of the novel neuro regenerative potential of ketamine has kindled great excitement and intrigue within the field of biological psychiatry. Early evidence indicates that ketamine might be able to repair brain damage caused by various mental illnesses by accelerating neural growth, enhancing repair processes, and promoting the branching of neurons [9]. Dendrites' sensing and transmission functions would be promptly rehabilitated, allowing for improved communication within the brain [10]. By regenerating numerous new dendrites and increasing the connections among brain cells, ketamine has the potential to rejuvenate a complex neural network in the brain, thereby aiding in the recovery of cognitive function [11]. Furthermore, it may correct cognitive distortions

by effectively regulating how individuals process and prioritize the information that they receive from the world surrounding them [12]. Theoretically, this rejuvenation helps patients establish new and accurate mental models about life, especially during the comprehensive rehabilitation process of both depression and the accompanying cognitive distortions [13]. This innovative approach suggests a new frontier in treatment possibilities for those struggling with mental health issues, highlighting ketamine's transformative capabilities in therapeutic settings.

However, many critical scientific predecessors work must be done before translating the potential neuroplasticity benefits into clinical benefits. The current limited extent of knowledge on the therapeutic mechanisms of ketamine, the understanding of neuron biology, the determination of underlying environmental regulatory factors of ketamine use, and the research on ketamine formulation specifications for better therapeutic efficacy with the least adverse consequences are only at a preliminary state. Consequently, the findings will facilitate the development of new pharmacological and neuromodulation treatment strategies for depression through promoting cognitive and emotional plasticity, in tandem with other psychotherapeutic, neuromodulator, or memory retrieval consolidation strategies. This review focuses on the neuro-regenerative potential of ketamine in the repair of emotional, cognitive, and physical impairments in patients with depression, both in preclinical subjects and human studies.

Understanding Depression and Current Treatment Modalities

The mental illness depression is the second leading cause of disability worldwide [14]. It is now well-established that clinical depression arises from a complex interaction of various factors including genetic, psychological, environmental, and biological [15]. As the name suggests, major depression is characterized by several symptoms that persist over a long period and reduce the affected person's ability to function. Symptoms of depression are grouped into categories such as mood, cognitive, physiological, and others [16]. Symptoms included in the mood category are low mood, and physical and mental fatigue leading to feelings of tiredness and death wishes [16]. Symptoms included in the cognitive domain are pessimistic thinking, poor concentration, reduced memory, and induction of suicidal thoughts [17]. The last categories, except for the cognitive category, deal with physical bodily changes [18].

The three most frequently used treatment modalities for depression are pharmacotherapy, psychotherapy, and mood stimulation [19]. The majority of current therapeutic agents for major depressive disorder work by increasing neurotrophic signaling, which then promotes neuronal survival [20]. However, most of the currently available therapeutic agents take considerable time to exhibit their beneficial effects [21]. This lag in therapeutic onset adds to the morbidity of the people who need treatment and increases the cost of care. Additionally, together with the lag in the onset of action, it is now recognized that at least 50% of people go into remission from depression following their first antidepressant treatment [22]. This illustrates the need for the identification of newer treatment possibilities for people suffering from depression. The ideal antidepressant should positively influence symptoms, improve mood, restore normal bodily function, and importantly, enhance cognitive performance. It is imperative to use therapeutic agents that, when used in conjunction with other non-pharmacological therapeutic agents and through therapy, induce faster remission.

Treatment options that include supplementary non-replicable use of agents that can upregulate neurotrophic factors at a faster rate are sought [23]. In recent years, there has been increased interest in the ability of low-dose ketamine to be used as an antidepressant in animal models of depression and individuals suffering from major depressive disorder [24]. In this chapter, we explore the potential of low doses of ketamine to be used as a neurotrophic enhancement therapeutic agent, it is well established that antidepressants that induce a therapeutic effect faster than current conventional antidepressants do improve cognitive and memory dimensions, which are subject to decline in major depressive disorder [25]. We began by describing the cellular changes that have been associated with the pathogenesis of major depressive disorder. Then we outline a brief description of what ketamine is, its current clinical use, and how it might be used in animal models of major depressive disorder. We then explore the neurogenesis progression in the dentate gyrus of the hippocampus and the prefrontal cortex. We end by contemplating the mechanistic pathways that ketamine uses to act as an antidepressant.

The Role of Ketamine in Neuroregeneration

Preclinical and clinical studies suggest that ketamine, a non-competitive N-methyl-D-aspartate receptor antagonist [26], has a unique rapid antidepressant effect [27]. Over the past decade, mounting evidence from clinical and preclinical studies has demonstrated that ketamine also exerts neurorestorative effects accompanied by synapse formation and neuronal regeneration in several limbic circuits and brain regions [28]. Clinical improvement in depressed patients is seen hours after the ketamine challenge [28]. Preclinical work conducted in rodents indicated that the ketamine-induced increase of synaptic protein levels at the spine level in the CA3 hippocampus and the prefrontal cortex contributes to this unique mechanism of rapid antidepressant effect that may be due to increased dendrite spine density and synaptic function [28].

The synaptic plasticity hypothesis builds the relationship between animal cognition, typical depression-like behavior, and the mouse and rat models of synaptic plasticity [29]. Reduced synaptic plasticity, along with reduced neurogenesis, impairment or regulation of monoamine release, and inflammatory pathways in the hippocampus and the prefrontal cortex, is proposed as representative of the brain pathology associated with depression [30]. It is hypothesized that any intervention increasing these pathways of neuroregeneration would lead to emotional and cognitive recovery [31]. Several molecular and cellular changes lead to depression amelioration and consistent repair of cognitive function [32]. These include synaptic protein, dendritic number and length, the ratio of excitatory glutamatergic relative number, functional measures—long-term potentiation ratio, and increased measures of overall hippocampal volume, and long-term potential for evoked responses [10]. Taken together, drugs rapidly improving synaptic plasticity and neurogenesis would be expected to promote a rapid recovery of emotional symptoms as well as repair cognitive function [33].

Neurobiological Mechanisms of Ketamine's Action in Depression

It is still not well understood how ketamine may lead to therapeutic actions in mood disorders [34]. The data from clinical trials aimed at elaborating the hypotheses are indeed promising, yet modest. Nevertheless, the most recent meta-analyses and systematic reviews, including fMRI and PET studies, contributed to a better understanding and elaborated several key findings on the mechanisms of ketamine's action in TRD [35]. The key principle of ketamine's action is NMDA blockage [36]. Ketamine binds within the channel of the NMDAR, providing superior structural stability compared to other NMDA antagonists [37]. Ketamine has over 15 times the affinity for NMDA receptor units when compared to other NMDAR antagonists [38]. Ketamine infusion leads to a rapid increase in NMDAR tonic inhibition in the cortex and GABAergic interneurons of prefrontal and limbic structures [39].

Ketamine demonstrates a high affinity for extra synaptic NMDAR [37]. These sites are involved in the molecular cascade leading to synaptic damage, as demonstrated in Alzheimer's disease and dementia [40]. Co-administration of NMDAR co-agonists prevents hippocampal spine degeneration and has shown antidepressant effects, serving as a translational animal model [41]. Co-administration of NMDA receptor activation and prevention of dysfunction can provide extra synaptic plasticity, easing the repair and synaptic strengthening process [42]. Flow MRI studies have shown reduced glutathione levels in the anterior cingulate gyrus [43]. MRS studies demonstrated the effect: of reduced glutamatergic effects, including decreased levels of glutamate and glutamine, and increased synaptic levels of glutamate [44].

Clinical Evidence Supporting Ketamine's Efficacy in Depression

Depression is a serious mental illness that, if recurrent or chronic, significantly affects the quality of life and functional prognosis of affected individuals, greatly impacting families, friends, and communities [45]. In this context, the pharmacological treatment of depression presents significant limitations due to the time required for the manifestation of therapeutic proof of concepts and the low or partial response to available therapies (Sepulveda Ramos, C., 2022). Ketamine hydrochloride is a substance classified as a general anesthetic [46, 47], acting primarily as a non-competitive antagonist of the N-methyl-D-aspartate receptor, in addition to producing dissociative, hallucinogenic, analgesic, and amnesic effects [26]. In anesthesia, ketamine is used in subanesthetic dosages because it provides relaxation, maintaining spontaneous airways and cardiocirculatory dynamic stability, reflecting in the activity of brainstem structures [48]. Patients suffering from TRD exhibited rapid and robust antidepressant effects after a single intravenous subanesthetic ketamine administration [49]. Several studies have demonstrated the rapid and highly effective response to intravenous ketamine in the treatment of major depression, mainly unipolar and bipolar depression, as well as depression associated with the diagnosis of borderline personality disorder [50]. Given its very limited response latency, ketamine has been noted to favor aggressiveness as well as help patients who express the urgency of committing suicide [51, 52]. These potential protective and therapeutic effects of acute ketamine administration are relevant to mediate the clinical strategies previously described in global strategy policies for the prevention and control of self-harm that prioritize earlier improvement and evaluate the initiation of antidepressant action [53, 54]. The therapeutic advantage described to address the depressive phase of bipolar disorder characterizes ketamine as a unique psychotropic medication in mood disorders, given that lithium carbonate, selective serotonin reuptake inhibitors, venlafaxine, and clozapine do not present that indication [55].

Cognitive and Emotional Rehabilitation Effects of Ketamine

The phenomenology of mood symptoms following antidepressant treatment has been demonstrated by monitoring the improvement symptoms in patients who respond to treatment [56]. Improvement in negative affect is expected, and it has been suggested that mood and emotionally valanced experience generally operate on a vertical dimension graded by emotional intensity rather than inherent valence [57]. When treating treatment-resistant depressed patients with IV ketamine, the ability of subjects to occasionally enter hypomanic symptoms, such as feeling a surge of inspiration and a sense that things are finally getting better, has been considered the first indication that the drug is working [58].

This subjective impression has led to the hypothesis that positive mood symptoms accompanying ketamine treatment in depression may have a hypomanic-like aura.

Ketamine’s rapid onset targets people’s most desperate and urgent depressive complaints [59]. If we count days rather than weeks, where a single day’s absence can feel endless to a suicidal patient, the reliable relief of preoccupying anxiety is remarkable [60]. In addition, similarly timed relief of associated physical symptoms, such as appetite and sleep, may accompany reversible symptomatic improvements induced by ketamine in patients with major depressive disorder and bipolar depression [53]. It is proved that Montgomery–Asberg Depression Rating scale’s item for anhedonia improved by 63%, concentration improved by 58.3%, item for suicidal ideation improved by 64.7% at 24 h compared to baseline following a single infusion of ketamine in patients with TRD [54] . As a result, in clinical experience as shown in (Figure 1), the situational anxiety, tension, and specific symptoms associated with suicide that accompanies baseline tension may respond better and more rapidly to ketamine treatment than do the nonmotivational negative affect, low energy, depressive affect, anhedonia, and mood-related symptoms of depression alone (Cui et al., 2024).

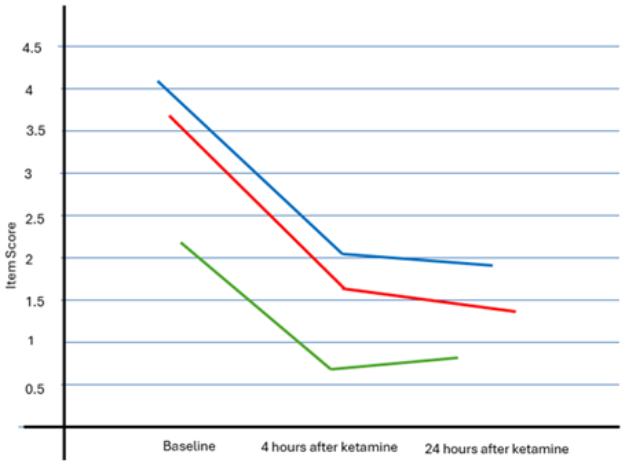

Figure 1: Evaluation for anhedonia (red), concentration (green), and suicidality (blue). The data obtained from a randomized controlled trial (RCT) that included 72 patients with treatment-resistant depression (TRD) [54].

Future Directions and Implications for Research and Clinical Practice

In summary, the clinical, preclinical, and translational research findings presented support the hypothesis that ketamine exerts neurobehavioral restorative effects in depression by reversing stress-induced atrophy and increasing the density and functionality of excitatory synaptic signaling [61]. Future directions consist of the design of clinical studies to determine the clinical benefits of ketamine treatment on core depressive symptoms and cognitive impairments, prediction of response, identification of pharmacological or transcranial biophysical mechanisms that support rapid recovery of brain function, and assessment of the effectiveness of chemical and non-chemical single and maintenance strategies to maintain cognition. The neurochemical profile of an individual may play an important role in determining the clinical efficacy and adverse effects of ketamine and the use of specific excitatory neurotransmission-enhancing agents to more effectively treat refractory patients. Non-pharmacological treatments may have added clinical value by enhancing excitatory signaling and brain recovery in patients with depression.

A further understanding of the impact of ketamine on resilience, creating or strengthening neuronal plasticity, and its role in defeating negative processing or repairing the experience of traumatic events and neuroendocrine changes during early life will also be crucial. The restoration of granule cell functions in the mice during the long-term evaluation will help determine the long-term impact of ketamine on the development and hippocampal functions in people whose brains are not mature. Analysis of the toxicity of antidepressants in the treatment of depressive mice should also be considered to better understand the potential therapeutic benefits of using ketamine in depressive children or adolescents.

Conclusion

It is important to address the interesting question of the applicability of the role of ketamine in restoring cognitive and emotional abilities in the context of bipolar-like depression. Such studies will help identify previously unexplored therapeutic targets of major depressive disorders and thus promote the development of more effective treatments.

References

1. Gill, H., Gill, B., Rodrigues, N. B., Lipsitz, O., Rosenblat, J. D., El-Halabi, S., ... & McIntyre, R. S. (2021). The effects of ketamine on cognition in treatment-resistant depression: a systematic review and priority avenues for future research. Neuroscience & Biobehavioral Reviews, 120, 78-85.
2. Daly, E. J., Trivedi, M. H., Janik, A., Li, H., Zhang, Y., Li, X., ... & Singh, J. B. (2019). Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. JAMA psychiatry, 76(9), 893-903.
3. Fava, M., Freeman, M. P., Flynn, M., Judge, H., Hoeppner, B. B., Cusin, C., ... & Papakostas, G. I. (2020). Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Molecular psychiatry, 25(7), 1592-1603.
4. Leal, G. C., Bandeira, I. D., Correia-Melo, F. S., Telles, M., Mello, R. P., Vieira, F., ... & Quarantini, L. C. (2021). Intravenous arketamine for treatment-resistant depression: open-label pilot study. European archives of psychiatry and clinical neuroscience, 271, 577-582.
5. Aan Het Rot, M., Zarate Jr, C. A., Charney, D. S., Mathew, S. J. (2012). Ketamine for depression: where do we go from here?. Biological psychiatry, 72(7), 537-547.
6. Singh, J. B., Fedgchin, M., Daly, E. J., De Boer, P., Cooper, K., Lim, P., ... & Van Nueten, L. (2016). A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. American Journal of Psychiatry, 173(8), 816-826.
7. Singh, I., Morgan, C., Curran, V., Nutt, D., Schlag, A., McShane, R. (2017). Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. The Lancet Psychiatry, 4(5), 419-426.

8. Riggs, L. M., Gould, T. D. (2021). Ketamine and the future of rapid-acting antidepressants. Annual Review of Clinical Psychology, 17(1), 207-231.
9. Muscat, S. A., Hartelius, G., Crouch, C. R., Morin, K. W. (2021). An integrative approach to ketamine therapy may enhance multiple dimensions of efficacy: improving therapeutic outcomes with treatment resistant depression. Frontiers in Psychiatry, 12, 710338.
10. Runge, K., Cardoso, C., De Chevigny, A. (2020). Dendritic spine plasticity: function and mechanisms. Frontiers in synaptic neuroscience, 12, 36.
11. Wu, H., Savalia, N. K., Kwan, A. C. (2021). Ketamine for a boost of neural plasticity: how, but also when?. Biological psychiatry, 89(11), 1030-1032.
12. Villalobos, D., Pacios, J., Vázquez, C. (2021). Cognitive control, cognitive biases and emotion regulation in depression: a new proposal for an integrative interplay model. Frontiers in Psychology, 12, 628416.
13. Kora, M. (2024). Foundational Principles Behind Cognitive-Behavioral Therapies. Ceres Yayınları.
14. Salleh, M. R. (2018). The burden of mental illness: An emerging global disaster. Journal of Clinical and Health Sciences, 3(1), 1-8.
15. Pitsillou, E., Bresnehan, S. M., Kagarakis, E. A., Wijoyo, S. J., Liang, J., Hung, A., & Karagiannis, T. C. (2020). The cellular and molecular basis of major depressive disorder: towards a unified model for understanding clinical depression. Molecular biology reports, 47, 753-770.
16. Chand, S. P., Arif, H. (2022). Depression. In StatPearls. StatPearls Publishing.
17. Perini, G., Cotta Ramusino, M., Sinforiani, E., Bernini, S., Petrachi, R., & Costa, A. (2019). Cognitive impairment in depression: recent advances and novel treatments. Neuropsychiatric disease and treatment, 1249-1258.
18. Rosch, E., Lloyd, B. B. (Eds.). (2024). Cognition and categorization. Taylor & Francis.
19. Bayes, A. J., Parker, G. B. (2018). Comparison of guidelines for the treatment of unipolar depression: a focus on pharmacotherapy and neurostimulation. Acta Psychiatrica Scandinavica, 137(6), 459-471.
20. Correia, A. S., Cardoso, A., Vale, N. (2023). BDNF unveiled: exploring its role in major depression disorder serotonergic imbalance and associated stress conditions. Pharmaceutics, 15(8), 2081.
21. Gaynes, B. N., Lux, L., Gartlehner, G., Asher, G., Forman-Hoffman, V., Green, J., ... & Lohr, K. N. (2020). Defining treatment-resistant depression. Depression and anxiety, 37(2), 134-145.
22. Malhi, G. S., Morris, G., Bell, E., Hamilton, A. (2020). A new paradigm for achieving a rapid antidepressant response. Drugs, 80(8), 755-764.
23. Schosser, A. (2020). Brain derived neurotrophic factor-genetic and epigenetic mechanisms with relevance to the major depressive disorder and suicide phenotypes (Doctoral Thesis).
24. Kohtala, S. (2021). Ketamine—50 years in use: from anesthesia to rapid antidepressant effects and neurobiological mechanisms. Pharmacological Reports, 73(2), 323-345.
25. Jawad, M. Y., Di Vincenzo, J. D., Badulescu, S., Teopiz, K. M., Tabassum, A., Ceban, F., ... & McIntyre, R. S. (2023). The therapeutic role of ketamine and esketamine in treating psychopathological domains of depression. Neuropharmacology, 223, 109299.
26. Al-Gailani, L., Al-Kaleel, A., Arslan, G., Ayyıldız, M., Ağar, E. (2022). The effect of general anesthetics on genetic absence epilepsy in WAG/Rij rats. Neurological Research, 44(11), 995-1005.
27. Shinohara, R., Aghajanian, G. K., Abdallah, C. G. (2021). Neurobiology of the rapid-acting antidepressant effects of ketamine: impact and opportunities. Biological Psychiatry, 90(2), 85-95.
28. Kim, J. W., Suzuki, K., Kavalali, E. T., Monteggia, L. M. (2023). Bridging rapid and sustained antidepressant effects of ketamine. Trends in molecular medicine, 29(5), 364-375.
29. Czéh, B., Simon, M. (2021). Benefits of animal models to understand the pathophysiology of depressive disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 106, 110049.
30. Levy, M. J., Boulle, F., Steinbusch, H. W., van den Hove, D. L., Kenis, G., Lanfumey, L. (2018). Neurotrophic factors and neuroplasticity pathways in the pathophysiology and treatment of depression. Psychopharmacology, 235, 2195-2220.
31. Toricelli, M., Pereira, A. A. R., Abrao, G. S., Malerba, H. N., Maia, J., Buck, H. S., Viel, T. A. (2021). Mechanisms of neuroplasticity and brain degeneration: strategies for protection during the aging process. Neural regeneration research, 16(1), 58-67.
32. Fries, G. R., Saldana, V. A., Finnstein, J., Rein, T. (2023). Molecular pathways of major depressive disorder converge on the synapse. Molecular Psychiatry, 28(1), 284-297.
33. Olson, D. E. (2018). Psychoplastogens: a promising class of plasticity-promoting neurotherapeutics. Journal of experimental neuroscience, 12, 1179069518800508.
34. Kritzer, M. D., Mischel, N. A., Young, J. R., Lai, C. S., Masand, P. S., Szabo, S. T., Mathew, S. J. (2022). Ketamine for treatment of mood disorders and suicidality: a narrative review of recent progress. Annals of clinical psychiatry: official journal of the American Academy of Clinical Psychiatrists, 34(1), 33.
35. Zavaliangos-Petropulu, A., Al-Sharif, N. B., Taraku, B., Leaver, A. M., Sahib, A. K., Espinoza, R. T., Narr, K. L. (2023). Neuroimaging-derived biomarkers of the antidepressant effects of ketamine. Biological psychiatry: cognitive neuroscience and neuroimaging, 8(4), 361-386.
36. Zanos, P., Gould, T. D. (2018). Mechanisms of ketamine action as an antidepressant. Molecular psychiatry, 23(4), 801-811.
37. Abbott, J. A., Wen, H., Liu, B., Gupta, S. S., Iacobucci, G. J., Zheng, W., Popescu, G. K. (2024). Allosteric inhibition of NMDA receptors by low dose ketamine. Molecular Psychiatry, 1-10.
38. Thompson, T., Whiter, F., Gallop, K., Veronese, N., Solmi, M., Newton, P., Stubbs, B. (2019). NMDA receptor antagonists and pain relief: A meta-analysis of experimental trials. Neurology, 92(14), 1652-1662.
39. McMillan, R., Muthukumaraswamy, S. D. (2020). The neurophysiology of ketamine: an integrative review. Reviews in the Neurosciences, 31(5), 457-503.

40. Yu, S. P., Jiang, M. Q., Shim, S. S., Pourkhodadad, S., Wei, L. (2023). Extrasynaptic NMDA receptors in acute and chronic excitotoxicity: implications for preventive treatments of ischemic stroke and late-onset Alzheimer's disease. Molecular Neurodegeneration, 18(1), 43.
41. Seillier, C., Lesept, F., Toutirais, O., Potzeha, F., Blanc, M., Vivien, D. (2022). Targeting NMDA receptors at the neurovascular unit: Past and future treatments for central nervous system diseases. International journal of molecular sciences, 23(18), 10336.
42. Chakraborty, P., Dey, A., Gopalakrishnan, A. V., Swati, K., Ojha, S., Prakash, A., ... & Dewanjee, S. (2023). Glutamatergic neurotransmission: A potential pharmacotherapeutic target for the treatment of cognitive disorders. Ageing Research Reviews, 85, 101838.
43. Poletti, S., Paolini, M., Mazza, M. G., Palladini, M., Furlan, R., Querini, P. R., ... & Covid BioB Outpatients Clinic Study Group. (2022). Lower levels of glutathione in the anterior cingulate cortex associate with depressive symptoms and white matter hyperintensities in COVID-19 survivors. European Neuropsychopharmacology, 61, 71-77.
44. Duarte, J. M., Xin, L. (2019). Magnetic resonance spectroscopy in schizophrenia: evidence for glutamatergic dysfunction and impaired energy metabolism. Neurochemical research, 44, 102-116.
45. Bains, N., Abdijadid, S. (2022). Major Depressive Disorder. In StatPearls. StatPearls Publishing.
46. Al Kaleel, A., Erbaş, O., Aygün, H. (2022). The effect of Madopar on absence like seizures in WAG/Rij rats. Acta Neurobiologiae Experimentalis, 82(1), 88-95.
47. Al-Gailani, L., Al-Kaleel, A., Arslan, G., Ayyıldız, M., Ağar, E. (2022). The effect of general anesthetics on genetic absence epilepsy in WAG/Rij rats. Neurological Research, 44(11), 995-1005.
48. Al-Kaleel, A., Aygun, H., Al-Gailani, L., Kabak, Y., Inal, S., Ayyildiz, M., ... & Agar, E. (2023). The electrophysiological and behavioral evaluation of the peptide hemopressin and cannabinoid CB1 receptor agonist and antagonist in pentylenetetrazol model of epilepsy in rats. Pflügers Archiv-European Journal of Physiology, 475(6), 719-730.
49. Zheng, W., Yang, X. H., Gu, L. M., Tan, J. Q., Zhou, Y. L., Wang, C. Y., Ning, Y. P. (2022). Antianhedonic effects of serial intravenous subanaesthetic ketamine in anxious versus nonanxious depression. Journal of Affective Disorders, 313, 72-76.
50. Fancy, F., Haikazian, S., Johnson, D. E., Chen-Li, D. C., Levinta, A., Husain, M. I., ... & Rosenblat, J. D. (2023). Ketamine for bipolar depression: an updated systematic review. Therapeutic Advances in Psychopharmacology, 13, 20451253231202723.
51. Chammas, F., Januel, D., Bouaziz, N. (2022). Inpatient suicide in psychiatric settings: Evaluation of current prevention measures. Frontiers in psychiatry, 13, 997974.
52. Murrough, J. W., Perez, A. M., Pillemer, S., Stern, J., Parides, M. K., aan het Rot, M., ... & Iosifescu, D. V. (2013). Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biological psychiatry, 74(4), 250-256.
53. Cui, L., Li, S., Wang, S., Wu, X., Liu, Y., Yu, W., ... & Li, B. (2024). Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduction and Targeted Therapy, 9(1), 30.
54. DeWilde, K. E., Levitch, C. F., Murrough, J. W., Mathew, S. J., Iosifescu, D. V. (2015). The promise of ketamine for treatment-resistant depression: current evidence and future directions. Annals of the New York Academy of Sciences, 1345(1), 47-58.
55. Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., …& Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar disorders, 20(2), 97–170.
56. Jerotić, S., Ivković, M. (2024). Pharmacological treatment of treatment-resistant depression: Towards evidence-based recommendations. Medicinska istraživanja, 57(1), 59-66.
57. 57. Megalakaki, O., Ballenghein, U., Baccino, T. (2019). Effects of valence and emotional intensity on the comprehension and memorization of texts. Frontiers in Psychology, 10, 179.
58. Krystal, J. H., Kavalali, E. T., Monteggia, L. M. (2024). Ketamine and rapid antidepressant action: new treatments and novel synaptic signaling mechanisms. Neuropsychopharmacology, 49(1), 41-50.
59. Jawad, M. Y., Qasim, S., Ni, M., Guo, Z., Di Vincenzo, J. D., d'Andrea, G., ... & McIntyre, R. S. (2023). The role of ketamine in the treatment of bipolar depression: a scoping review. Brain Sciences, 13(6), 909.
60. Han, B., Crosby, A. E., Ortega, L. A., Parks, S. E., Compton, W. M., Gfroerer, J. (2016). Suicidal ideation, suicide attempt, and occupations among employed adults aged 18–64 years in the United States. Comprehensive psychiatry, 66, 176-186.
61. Krystal, J. H., Kaye, A. P., Jefferson, S., Girgenti, M. J., Wilkinson, S. T., Sanacora, G., Esterlis, I. (2023). Ketamine and the neurobiology of depression: Toward next-generation rapid-acting antidepressant treatments. Proceedings of the National Academy of Sciences, 120(49), 2305772120.