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Basic aspects of ketamine therapy for treatment-resistant depression - a review paper

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Abstract

Introduction and purpose: Major depressive disorder (MDD) is the most common psychiatric illness, affecting millions of people worldwide. The first line of pharmacological treatment is usually monoamine reuptake inhibitors. Up to 60% of cases, may be drug-

resistant patients, prompting researchers to research substances other than conventional. [1] The purpose of this article was to review recent studies on the use of ketamine in the treatment of drug-resistant depression and present their findings.

Brief description of the state of knowledge: Ketamine has been a well-known drug used in anesthesiology and pain management for decades. Because of its multidirectional effects, researchers have become interested in its effects on psychiatric illnesses. Over the past decade or so, there has been a definite increase in research and articles on the use of ketamine in psychiatry. The study has resulted in FDA approval of esketamine for the treatment of treatment-resistant depression in adults in 2019.

Material and method: This article is the result of searching keywords on databases such as Google Scholar and Pubmed and collecting scientific literature about depression and ketamine. Articles were preselected by title, number of citations, source, and publication date.

Summary: Ketamine has the potential to be a treatment for drug-resistant depression. Its effectiveness varies with the form and dosage, with racemic and higher doses offering greater therapeutic benefits. Ketamine's efficacy is on par with the electroconvulsive therapy. Its onset is faster than traditional antidepressants, significantly reducing suicide risk in a shorter time frame. While the precise mechanisms of its antidepressant effects are not fully understood, it is suggested that its impact on brain neuroplasticity may contribute to the rapid onset of action. Growing evidence supports ketamine's effectiveness in treating TRD, highlighting the need for further research in this area.

Keywords: ketamine, depression, treatment-resistant, antidepressant, neuronal plasticity

Introduction

Major depressive disorder (MDD) is the most prevalent psychiatric disorder, representing a relevant cause of disability worldwide and determining a high burden for health systems (World Health Organization, 2017) [3,4], affecting over 300 million people worldwide. [5] According to Beck's triad, individuals in depression have negative thoughts about the world,

themselves and the future which is the root of the disease. These beliefs lead to feelings such as sadness, hopelessness, emptiness, or irritation. [6] People in depression may experience things such as cognitive impairment, mood fluctuations, disrupted sleep patterns, loss of interest, fatigue, changes in appetite, or in the worst case suicidal thoughts and intentions. [7] Depression often has a significant interference with the patient's quality of life, which includes aspects such as social interactions, daily activities, and work. [8] MDD can be classified as mild, moderate, or severe, [9] depending on the number and intensity of symptoms and the degree to which they impair the individual's daily functioning. Depression significantly contributes to the global burden of disease, partly due to ineffective treatment. [7] The first-line pharmacotherapy for most patients with depression involves the use of drugs that act by inhibiting monoamine reuptake such as selective serotonin reuptake inhibitors (SSRIs) or selective serotonin-noradrenaline reuptake inhibitors (SNRIs). [10] While SSRIs are the basis of treatment, some patients do not respond to initial monotherapy and require a combination of antidepressants and psychotherapy, switching the drug or adding other pharmacological agents to increase efficacy. [4] Some researches indicated that if patients do not show a clinical response within a year, only 20% of them will respond to treatment over the next four years. [11] About 30% of patients are considered to have treatment-resistant depression (TRD), defined as an insufficient response to two more adequate trials of antidepressant medications. [12,13] For this reason, it is worth focusing on new therapies based on other potential mechanisms of depression development beyond the serotonin theory. [14] One of the recently widely studied substances with potential multidirectional antidepressant effects beyond its effects on serotonin pathways is ketamine. [15]

The aim

This article aims to provide a concise overview of the benefits brought by ketamine therapy in drug-resistant depression, based on studies in recent years that have looked at various aspects of ketamine's effects, and to raise awareness about other lines of treatment than previously known therapies such as the use of serotonin reuptake inhibitors or electroconvulsive therapy.

Materials and methods

Material for the article was searched on websites such as PubMed and GoogleScoolar, using the listed keywords. The first step was a selection based on the title, considering the source, number of citations, and date of publication. After reading the potential scientific literature, papers were finally selected that were the best fit for this article, i.e. to present general theory and research from recent years on different aspects of ketamine use.

Mechanisms of depression

The underlying pathophysiologic basis of depression, which led to the rapid development of serotonin reuptake inhibitor drugs, is a chemical imbalance in the brain - the monoamine hypothesis. [16] This idea originated in the late 1950s and early 1960s, assuming that depressive symptoms are caused by insufficient levels of serotonin, norepinephrine, and/or dopamine. [17] Scientists have observed that mood can be artificially influenced using medications – those that increased monoamine levels improved mood, while those that decreased amine levels led to depression. [18] Over time as antidepressants were used, molecular events following direct drug effects on monoamines began to be investigated. This allowed an immense degree of similarity to be observed between the molecular and cellular changes induced by antidepressant treatment and the molecular mechanisms of neuroplasticity, particularly synaptic plasticity, giving a new direction to the search for the pathophysiology and treatment of depression. [19] Neuroplasticity includes processes that modify brain structure, such as early synaptic plasticity, synapse formation or retraction, spinogenesis, synaptogenesis, axonal sprouting, axon regeneration, dendrite growth and formation, and even neurogenesis. [20] Neuroplasticity has been linked to factors such as increasing presynaptic glutamate release and brain-derived neurotrophic factor (BDNF) or modulating mTOR signaling. [21]

Ketamine

Ketamine was first synthesized as a derivative of phencyclidine in 1962. [22] Initially, it was used as an anesthetic, and later its application was expanded to include analgesia. [23] Ketamine is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is a type of glutamate receptor and a key excitatory neurotransmitter in the brain. [24] It exists in the form of two enantiomers racemic ketamine and esketamine. [25,26] In the past two decades, numerous RCTs have confirmed ketamine has rapid-onset antidepressant effects, unlike

conventional interventions including antidepressants, cognitive behavioral therapy, and electroconvulsive therapy that are reported to have effects in weeks. [27,28] Replicated evidence also indicates that ketamine can reduce aspects of suicidality within a few hours or in some patients as soon as 40 minutes after the infusion. [29,30] An antidepressant effect is possibly generated by modulating the coordination of glutamatergic communication as an NMDA and AMPA receptors and the release of brain-derived neurotrophic factor (BDNF) and the activation of mammalian target of rapamycin (mTOR) in the frontal network, [12,31] which are considered to affect neuroplasticity. Ketamine also has strong and fast-acting anti-inflammatory properties that may play a significant role in its antidepressant effects. Multiple studies have shown that ketamine suppresses the production of pro-inflammatory cytokines, such as IL-1β and TNF-α, and reduces the expression of NF-κB, a key inflammatory transcription factor. [32] Apart from that neuroimaging studies indicate ketamine's ability to alter glucose metabolism in regions associated with mood disorders. [33] Because of this possible multidirectional effect, which may have a beneficial effect on depressive symptoms, and growing reports on the subject, the FDA approved esketamine in intranasal spray form in 2019 for the treatment of drug-resistant depression in adults. [2]

Ketamine compared to Electroconvulsive Therapy for treatment-resistant major depression without psychosis

The (Anand et al. 2023) study conducted an open-label, randomized, noninferiority trial involving patients referred to ECT (Electroconvulsive Therapy) clinics for treatment-resistant major depression without psychosis. 195 patients received ketamine while 170 patients underwent ECT. During an initial 3-week treatment phase, patients received either ECT three times per week or ketamine (0.5 mg per kilogram of body weight over a 40-minute period) twice per week. The primary outcome was a response to treatment according to QIDS-SR16 and secondary outcomes included scores on memory tests and patient-reported quality of life (MADRS, QIDS-SR16, CGI-I, PGI-I, GSE-My, SMCQ, HVLT-R, CADSS). Following the initial treatment phase, patients who responded to the treatment were monitored for a period of 6 months. There was a response observed in 55.4% of patients who were administered ketamine and 41.2% of those treated with ECT. ECT appeared to cause a decrease in memory recall after 3 weeks of treatment, with gradual recovery observed during the follow-up period. Both trial groups had similar improvements in patient-reported quality of life. ECT was linked

to musculoskeletal side effects, whereas ketamine was associated with dissociative symptoms. The study confirmed that ketamine is as effective as ECT for treating treatment-resistant major depression without psychosis. [34]

Ketamine and antisuicidal effects

The (Grunebaum et al. 2018) research conducted a randomized clinical trial with 80 participants to compare the infusion of ketamine with midazolam in patients suffering from major depressive disorder who had clinically significant suicidal thoughts measured by the Scale for Suicidal Ideation (SSI). Participants were randomly allocated to receive an intravenous infusion of either racemic ketamine hydrochloride at a dose of 0.5 mg/kg or midazolam at a dose of 0.02 mg/kg, both in 100 mL of normal saline administered over a 40-minute period. Following evaluations at the 24-hour mark, participants were provided with optimized standard pharmacological treatment for six months, including weekly research assessments for the first six weeks during an uncontrolled follow-up observation. The primary outcome was the SSI score 24 hours post-infusion. Additional outcomes included overall depression ratings, clinical ratings during a 6-week open follow-up period, and safety evaluations. The proportion of responders on the SSI on day 1 was 55% for the ketamine group and 30% for the midazolam group. The reduction in suicidal ideation 230 minutes post-infusion was more significant in the ketamine group compared to the midazolam group. On day 1, the POMS total mood disturbance score, along with the depression and fatigue subscale scores, showed greater improvement in the ketamine group compared to the midazolam group. The proportions of responders in the ketamine and midazolam groups, respectively, were as follows: 30% vs. 15% on the 17-item HAM-D, 25% vs. 15% on the 24-item HAM-D, and 36% vs. 17% on the BDI. The improvement in suicidal ideation was largely maintained throughout the 6-week period of uncontrolled observation, during which standard pharmacological treatments were also optimized. These findings suggest that the observed advantage of ketamine over midazolam in reducing suicidal ideation 24 hours post-infusion is clinically significant. [35]

Ketamine's effect on neuroplasticity

In the (Kopelman et al. 2023) study, 98 adults with depression who had not responded to at least one antidepressant treatment were randomized in a 2:1 ratio to receive a single intravenous infusion of either ketamine (0.5 mg/kg) or saline. Participants also completed diffusion tensor imaging (DTI) assessments, as a presumptive marker of microstructural neuroplasticity in gray matter, at baseline before the infusion and 24 hours post-infusion. It was calculated for 7 regions of interest (left and right BA10, amygdala, and hippocampus; and ventral Anterior Cingulate Cortex) and compared to clinical response measured with MADRS and the QIDS-SR. Individual variations in DTI-MD change (with a greater decrease from baseline to 24 hours post-infusion, indicating enhanced neuroplasticity) were linked to more substantial improvements in depression scores across multiple brain regions. In the left BA10 and left amygdala, these relationships were primarily driven by the ketamine group (group * DTI-MD interaction effects: $p = 0.016–0.082$). In the right BA10, these associations were observed in both infusion groups ($p = 0.007$). In the left and right hippocampus, on the MADRS only, interaction effects were seen in the opposite direction, where DTI-MD change was inversely associated with depression change specifically in the ketamine group (group * DTI-MD interaction effects: $p = 0.032–0.06$). In conclusion, the immediate effects of ketamine on depression may be partially mediated by acute changes in neuroplasticity measurable with DTI. [36]

Ketamine speeds up the antidepressant effect of oral antidepressants

The (Hu et al. 2016) study was conducted between September 2013 and December 2014 where 30 outpatients with severe MDD were randomized to 4 weeks of double-blind treatment with escitalopram 10 mg/day + single-dose i.v. ketamine (0.5 mg/kg over 40 min) or escitalopram 10 mg/day + placebo (0.9% i.v. saline). MADRS, QIDS-SR, BPRS, YMRS, and CADSS scales were used for assessment in the study. Patients were evaluated at baseline, 1, 2, 4, 24, and 72 h and 7, 14, 21 and 28 days. The primary outcome was the time of response. Secondary outcomes were the percentage of participants who responded or achieved remission in each group, assessing the severity of depressive symptoms as rated by investigators and self-reported by participants, evaluating suicidal thoughts, reporting side effects, as well as the severity of manic, psychotic, and dissociative symptoms. At week 4, the cumulative response rate was 57.1% v. 92.3% with an average time to respond 26.5 ± 4.0 v. 6.4 ± 9.5 days in the escitalopram + placebo and escitalopram + i.v. ketamine groups. For

patients with treatment-resistant depression, the response rate was 33.3% in the escitalopram + placebo group and 88.9% in the escitalopram + ketamine group, and the average time to response was 28.0 ± 0.0 v. 8.9 ± 10.6 days,. At week 4, the cumulative remission rate was 14.3% v. 76.9% in the escitalopram + placebo and escitalopram + i.v. ketamine groups and the average time to remission was 27.0 ± 3.7 v. 14.0 ± 12.0 days. In the subgroup with treatment-resistant depression, the cumulative remission rate was 0% v. 66.7% in the escitalopram + placebo and escitalopram + i.v. ketamine groups. By week 4, there were no longer statistically important differences between the escitalopram + placebo and escitalopram + intravenous ketamine groups in terms of response rates and rates of remission. In conclusion single-dose i.v. ketamine augmentation of escitalopram has the potential to accelerate the early effectiveness of oral antidepressants in treating severe MDD. [37]

Racemic ketamine and esketamine

The (Nikolin et al. 2023) systematic review and meta-analysis was based on randomized controlled trials investigating ketamine for depression up to April 13, 2023. It analyzed 49 randomised controlled trials, comprising 3299 participants. Incorporating drug formulation (racemic or esketamine) and dose (low or high) as covariates, multivariable mixed-effects meta-regressions were performed. The effects of the treatment were evaluated: immediately after the first dose, throughout the repeated dosing period, and during follow-up after the final dose of the treatment course. Immediately following the first or single treatment, standardized mean differences (95% confidence intervals) were moderate to high across all conditions (Rac-High: −0.73, −0.91 to −0.56; Esket-High: −0.48, −0.75 to −0.20; Rac-Low: −0.33, −0.54 to −0.12; Esket-Low: −0.55, −0.87 to −0.24). Continued effects during repeated dosing were significantly greater compared to the control for Rac-High (−0.61; −1.02 to −0.20) and Rac-Low (−0.55, −1.09 to −0.00), but not for Esket-Low (−0.15, −0.49 to 0.19) or Esket-High (−0.22, −0.54 to 0.10). Upon further evaluation, the benefits continued to be noteworthy for racemic ketamine with a score of -0.65 (range: -1.23 to -0.07), but not for esketamine which scored at -0.33 (range: -96 to 31). Overall dropout rates due to any cause were similar between experimental and control conditions for both formulations combined (Odds Ratio = 1.18, 0.85–1.64). Heterogeneity ranged from 5.7% to 87.6% across the studies. This review indicated that racemic ketamine showed larger effect sizes in reducing depression severity, and higher response and remission rates compared to esketamine. Higher doses were more

effective than lower doses. Differences were observed in initial effects, continued treatment outcomes, and sustained effects following the final dose. [38]

Single and repeated ketamine infusions at the beginning of the therapy

The (Shiroma et al. 2020) randomized, double-blind, active placebo-controlled study was conducted between April 2015 and March 2019. The study involved 54 outpatients aged 18-75 with treatment-resistant depression and were divided into 2 groups in a 1:1 ratio. Patients received in 12 days five midazolam (0,045 mg/kg) infusions followed by single ketamine (0,5mg/kg) or six ketamine (0,5mg/kg) treatments and each infusion lasted 40 minutes. Study assessments were conducted on days 0, 1, 3, 5, 8, 10, and 12 to evaluate the safety and efficacy of ketamine compared to an active placebo during the infusion phase. After the end of the treatment evaluations were carried out weekly for the first 4 weeks, in 2-weeks intervals for the next 8 weeks, and then every 4 weeks for the remaining 12 weeks. The primary outcome was a change in depression severity measured by the MADRS score 24 hours after the last ketamine infusion. Secondary outcomes included changes in MADRS scores over time, response rates, remission rates, response and remission rates over time, and the durability of the response for up to 6 months. There was no significant difference between a single ketamine treatment (MADRS mean change = 21.0, 95% CI = 17.2–24.8) and six ketamine treatments (MADRS mean change = 17.2, 95% CI = 13.2–21.2) 24 hours after the final infusion. Prior to the last ketamine infusion, there were significant differences in MADRS scores in both groups in favor of the group with six ketamine infusions compared to midazolam. There was no statistically significant difference between the groups in terms of long-term remission - the 6-month relapse rates after the response was 75% (95% CI = 54.2–95.8%) and 68.4% (95% CI = 45.4–91.4%) for midazolam plus single ketamine and six ketamine group, respectively. However, the median time to relapse was 2 weeks for the midazolam plus single ketamine group, and 6 weeks for the six-ketamine group. In conclusion, ketamine showed efficacy compared to an active placebo, but due to the diminishing effect over time, more research is needed to discover the optimal frequency of ketamine administration so that it provides the greatest benefit. [39]

Summary

Based on the material presented, ketamine is a drug with potential in the treatment of drug-resistant depression. Its efficacy depends on the form and dose, where racemic and high doses provide greater therapeutic benefit. Multiple infusions of intravenous ketamine over a short period of time have not produced a better effect than a single ketamine infusion. Multiple infusions versus a single infusion of ketamine in the long-term antidepressant effect need more research. Ketamine's effectiveness is comparable to the use of electroconvulsive therapy. Ketamine has a faster onset of action than classic antidepressants and reduces the risk of suicide in a significantly shorter period of time. The mechanisms of antidepressant action are not fully understood, but it can be speculated that one of them responsible for the rapid onset is the effect on brain neuroplasticity. In conclusion, there is increasing evidence on the efficacy of ketamine in the treatment of drug-resistant depression, which justifies further research on this topic with more participants.

Disclosure

Author's contribution

Conceptualization: Weronika Szafrańska and Dominika Poborowska; methodology: Weronika Kahan; software: Tomasz Gańko; check: Katarzyna Polańska and Tomasz Gańko; formal analysis: Emilia Bąk and Oliwia Najjar; investigation: Jacek Fordymacki and Emilia Bąk; resources: Marta Wojaczek; data curation: Marta Wojaczek; writing - rough preparation: Weronika Kahan; writing - review and editing, Katarzyna Polańska; visualization: Jacek Fordymacki; supervision: Weronika Szafrańska and Dominika Poborowska; project administration, Emilia Bąk and Oliwia Najjar; receiving funding - no specific funding.

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The data presented in this study is available upon request from the corresponding author.

Conflict of interest

The authors deny any conflict of interest

References

1. DeWilde KE, Levitch CF, Murrough JW, Mathew SJ, Iosifescu DV. The promise of ketamine for treatment-resistant depression: current evidence and future directions. *Ann N Y Acad Sci*. 2015;1345(1):47-58. doi:10.1111/nyas.12646
2. Mansuri Z, Shah B, Yadav G, et al. Is Intravenous Ketamine Better Than Intranasal Esketamine for Treating Treatment-Resistant Depression? *Prim Care Companion CNS Disord*. 2024;26(1). doi:10.4088/PCC.23lr03607
3. Crisanti C, Enrico P, Fiorentini A, Delvecchio G, Brambilla P. Neurocognitive impact of ketamine treatment in major depressive disorder: A review on human and animal studies. *J Affect Disord*. 2020;276:1109-1118. doi:10.1016/j.jad.2020.07.119
4. Edinoff AN, Akuly HA, Hanna TA, et al. Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. *Neurol Int*. 2021;13(3):387-401. doi:10.3390/neurolint13030038
5. Dai D, Miller C, Valdivia V, et al. Neurocognitive effects of repeated ketamine infusion treatments in patients with treatment resistant depression: a retrospective chart review. *BMC Psychiatry*. 2022;22(1):140. doi:10.1186/s12888-022-03789-3

6. Belzung C, Willner P, Philippot P. Depression: from psychopathology to pathophysiology. *Curr Opin Neurobiol*. 2015;30:24-30. doi:10.1016/j.conb.2014.08.013
7. Sobin C. Psychomotor Symptoms of Depression. *M J Psychiatry*. Published online 1997.
8. Hofmann SG, Curtiss J, Carpenter JK, Kind S. Effect of treatments for depression on quality of life: a meta-analysis. *Cogn Behav Ther*. 2017;46(4):265-286. doi:10.1080/16506073.2017.1304445
9. Villarroel MA. Symptoms of Depression Among Adults: United States, 2019. 2020;(379).
10. Liu B, Liu J, Wang M, Zhang Y, Li L. From Serotonin to Neuroplasticity: Evolvement of Theories for Major Depressive Disorder. *Front Cell Neurosci*. 2017;11:305. doi:10.3389/fncel.2017.00305
11. Krystal JH, Kaye AP, Jefferson S, et al. Ketamine and the neurobiology of depression: Toward next-generation rapid-acting antidepressant treatments. *Proc Natl Acad Sci*. 2023;120(49):e2305772120. doi:10.1073/pnas.2305772120
12. Matveychuk D, Thomas RK, Swainson J, et al. Ketamine as an antidepressant: overview of its mechanisms of action and potential predictive biomarkers. *Ther Adv Psychopharmacol*. 2020;10:204512532091665. doi:10.1177/2045125320916657
13. Phillips JL, Norris S, Talbot J, et al. Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. *Neuropsychopharmacology*. 2020;45(4):606-612. doi:10.1038/s41386-019-0570-x
14. Lang UE, Borgwardt S. Molecular Mechanisms of Depression: Perspectives on New Treatment Strategies. *Cell Physiol Biochem*. 2013;31(6):761-777. doi:10.1159/000350094
15. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry*. 2018;23(4):801-811. doi:10.1038/mp.2017.255
16. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. *Mol Psychiatry*. 2023;28(8):3243-3256. doi:10.1038/s41380-022-01661-0
17. Delgado PL. Depression: The Case for a Monoamine Deficiency. *J Clin Psychiatry*.
18. Leo J, Lacasse JR. The Media and the Chemical Imbalance Theory of Depression. *Society*. 2008;45(1):35-45. doi:10.1007/s12115-007-9047-3
19. Pittenger C, Duman RS. Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms. *Neuropsychopharmacology*. 2008;33(1):88-109. doi:10.1038/sj.npp.1301574
20. Albert PR. Adult neuroplasticity: A new “cure” for major depression? *J Psychiatry*

Neurosci. 2019;44(3):147-150. doi:10.1503/jpn.190072

21. Huang YJ, Lane HY, Lin CH. New Treatment Strategies of Depression: Based on Mechanisms Related to Neuroplasticity. *Neural Plast*. 2017;2017:1-11. doi:10.1155/2017/4605971
22. Derakhshanian S, Zhou M, Rath A, et al. Role of Ketamine in the Treatment of Psychiatric Disorders. *Health Psychol Res*. 2021;9(1). doi:10.52965/001c.25091
23. Na KS, Kim YK. Increased use of ketamine for the treatment of depression: Benefits and concerns. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;104:110060. doi:10.1016/j.pnpbp.2020.110060
24. Zhang C, Xu Y, Zhang B, Hao W, Tang WK. Cognitive impairment in chronic ketamine abusers. *Psychiatry Res*. 2020;291:113206. doi:10.1016/j.psychres.2020.113206
25. Jelen LA, Young AH, Stone JM. Ketamine: A tale of two enantiomers. *J Psychopharmacol (Oxf)*. 2021;35(2):109-123. doi:10.1177/0269881120959644
26. Riggs LM, An X, Pereira EFR, Gould TD. (R,S)-ketamine and (2R,6R)-hydroxynorketamine differentially affect memory as a function of dosing frequency. *Transl Psychiatry*. 2021;11(1):583. doi:10.1038/s41398-021-01685-0
27. Abelaira HM, Réus GZ, Ignácio ZM, et al. Effects of ketamine administration on mTOR and reticulum stress signaling pathways in the brain after the infusion of rapamycin into prefrontal cortex. *J Psychiatr Res*. 2017;87:81-87. doi:10.1016/j.jpsychires.2016.12.002
28. Shen Z, Gao D, Lv X, Wang H, Yue W. A meta-analysis of the effects of ketamine on suicidal ideation in depression patients. *Transl Psychiatry*. 2024;14(1):248. doi:10.1038/s41398-024-02973-1
29. Karunarathna I, Kusumarathna K, Gunarathna I, et al. Ketamine: Mechanisms, Applications, and Future Directions.
30. Zhou Y, Wang C, Lan X, et al. Cognitive Function Mediates the Anti-suicide Effect of Repeated Intravenous Ketamine in Adult Patients With Suicidal Ideation. *Front Psychiatry*. 2022;13:779326. doi:10.3389/fpsyt.2022.779326
31. Murphy N, Tamman AJF, Lijffijt M, et al. Neural complexity EEG biomarkers of rapid and post-rapid ketamine effects in late-life treatment-resistant depression: a randomized control trial. *Neuropsychopharmacology*. 2023;48(11):1586-1593. doi:10.1038/s41386-023-01586-4
32. Hayley S, Litteljohn D. Neuroplasticity and the next wave of antidepressant strategies. *Front Cell Neurosci*. 2013;7. doi:10.3389/fncel.2013.00218

33. Li L, Vlisides PE. Ketamine: 50 Years of Modulating the Mind. *Front Hum Neurosci*. 2016;10. doi:10.3389/fnhum.2016.00612
34. Anand A, Mathew SJ, Sanacora G, et al. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. *N Engl J Med*. 2023;388(25):2315-2325. doi:10.1056/NEJMoa2302399
35. Grunebaum MF, Galfalvy HC, Choo TH, et al. Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial. *Am J Psychiatry*. 2018;175(4):327-335. doi:10.1176/appi.ajp.2017.17060647
36. Kopelman J, Keller TA, Panny B, et al. Rapid neuroplasticity changes and response to intravenous ketamine: a randomized controlled trial in treatment-resistant depression. *Transl Psychiatry*. 2023;13(1):159. doi:10.1038/s41398-023-02451-0
37. Hu YD, Xiang YT, Fang JX, et al. Single i.v. ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. *Psychol Med*. 2016;46(3):623-635. doi:10.1017/S0033291715002159
38. Nikolin S, Rodgers A, Schwaab A, et al. Ketamine for the treatment of major depression: a systematic review and meta-analysis. *eClinicalMedicine*. 2023;62:102127. doi:10.1016/j.eclinm.2023.102127
39. Shiroma PR, Thuras P, Wels J, et al. A randomized, double-blind, active placebo-controlled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. *Transl Psychiatry*. 2020;10(1):206. doi:10.1038/s41398-020-00897-0