*PSYCHIATRY*

Cite as: Archiv EuroMedica. 2024. 14; 6. DOI 10.35630/2024/14/6.611

***Received 12 November 2024;***
***Accepted 14 December 2024;***
***Published 17 December 2024***

# KETAMINE AND ESKETAMINE IN TREATMENT-RESISTANT DEPRESSION

***Jakub Prosowski*** ✉, ***Szczepan Pośpiech***, ***Michał Piotrowski***, ***Piotr Serwicki***, ***Jakub Początek***

*Medical University of Silesia, Katowice, Poland*

✉ ***jakubprosowski@gmail.com***

download article (pdf)

## ABSTRACT

Aims: This review aims to explore the efficacy, mechanisms, administration routes, and safety profiles of ketamine and esketamine in the treatment of treatment-resistant depression (TRD).

**Methods:** A comprehensive review of recent studies on ketamine and esketamine's therapeutic applications in TRD was conducted. Sources included randomized controlled trials, systematic reviews, and meta-analyses from PubMed and Google Scholar.

**Results:** Ketamine demonstrated rapid antidepressant effects within hours of administration, with symptom relief lasting several days to weeks. Esketamine, developed as an intranasal spray, provided an alternative route, improving accessibility while delivering therapeutic benefits. Additionally, ketamine has shown rapid effects on suicidal ideation, making it a viable option for crisis management in TRD patients. Both ketamine and esketamine enhance neuroplasticityby antagonizing NMDA receptors, leading to increased glutamate release, which activates AMPA receptors and promotes synaptogenesis. Clinical studies have shown that ketamine induces an immediate surge in brain-derived neurotrophic factor (BDNF) and upregulates the mTOR pathway, essential for the formation and strengthening of synaptic connections in mood-regulating brain regions. Although treatment is effective in the short-term, the data on long-term safety is scarce.

**Conclusions**: Ketamine and esketamine represent significant advancements in the treatment of TRD, offering rapid symptom relief and neuroplastic benefits not achieved with traditional antidepressants. Future studies are required to establish long-term safety profiles and optimize dosing regimens. Overall, ketamine-based therapies provide a promising alternative for patients unresponsive to conventional treatments.

Keywords: ketamine, esketamine, treatment-resistant depression, major depressive disorder, suicidal ideation, neuroplasticity

## INTRODUCTION

Major depressive disorder (MDD) is a prevalent and debilitating condition, significantly impacting individuals' well-being. Treatment-resistant depression (TRD), which affects up to one-third of individuals with MDD, poses a significant challenge in management of patients. The high number of non-responders, as well as the overall delayed therapeutic effect of standard first-line medications, motivated researchers to find alternative treatment options. Ketamine and its S-enantiomer, esketamine, have gained substantial attention due to their novel mechanisms of action.

## METHODS

A comprehensive review of recent studies on ketamine and esketamine's therapeutic applications in TRD was conducted from PubMed and Google Scholar. Sources included randomized controlled trials, systematic reviews, and meta-analyses examining clinical outcomes, pharmacodynamics, neuroplasticity effects, and safety concerns.

## RESULTS OF SELECTION

The selection process for this review included a search of relevant studies on ketamine and esketamine's use in treatment-resistant depression (TRD). Sources encompassed randomized controlled trials, systematic reviews, meta-analyses, and key clinical trials. The final selection prioritized studies that evaluated the antidepressant efficacy, mechanisms of action, insights into pharmacodynamics, and safety profiles of ketamine and esketamine in TRD. The search combined keywords and phrases, such as: "ketamine," "esketamine," "treatment-resistant depression," "TRD," "NMDA antagonist," "suicidal ideation," and "neuroplasticity." Focused on the use of ketamine or esketamine in treating TRD.

Studies were included if they:

- Reported clinical outcomes, such as depressive symptom relief, reduction in suicidal ideation, or improvements in neuroplasticity.
- Were peer-reviewed randomized controlled trials, systematic reviews, or meta-analyses.
- Provided insights into pharmacodynamics, safety, and neurobiological mechanisms.
- Studies were excluded if they:
- Focused solely on ketamine or esketamine's use in conditions other than TRD.
- Lacked clear outcome measures or did not directly evaluate the antidepressant efficacy or safety profile of ketamine or esketamine.
- Were non-peer-reviewed articles, case reports, or anecdotal evidence.

## CONTENT OF THE REVIEW

### TREATMENT-RESISTANT DEPRESSION

Unipolar major depressive disorder (MDD) is one of the most common mental-health disorders and affects approximately 350 million people worldwide, making it the leading cause of disability. It's associated with harmful consequences to the functioning of affected individuals and society.[23,31] Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly prescribed first-line therapies. However, while these drugs can be effective, they often have delayed onset times, requiring anywhere from 6 to 12 weeks to produce full therapeutic effects.[36] This delay can lead to extended periods of suffering for patients who remain symptomatic and may experience increased feelings of hopelessness, frustration, and potential risk for suicide during the waiting period. A critical challenge in treating MDD is the high prevalence of treatment resistance. Up to one-third of patients with MDD do not achieve adequate relief from standard antidepressant therapies, a condition defined as treatment-resistant depression (TRD).[7] TRD is typically diagnosed when a patient fails to respond to at least two different classes of antidepressant medications at adequate doses and treatment durations.[9] The persistence of depressive symptoms in TRD can severely impact a patient's quality of life. Individuals with TRD are at higher risk for both physical and mental comorbidities, including cardiovascular disease, obesity, chronic pain, and increased risk for suicide.[40 22] The lack of adequate response in TRD patients has driven a search for alternative treatment methods capable of delivering faster and more effective relief than conventional therapies.[37]

### INTRODUCTION TO KETAMINE AND ESKETAMINE

Among the alternative treatments that modulate other neurotransmitter systems. ketamine and its S-enantiomer, esketamine, have gained considerable interest. Ketamine is a glutamatergic *N*-methyl-d-aspartate (NDMA) receptor antagonist, on the WHO Essential Medicine List for use as an anaesthetic and prescribed off-label to treat chronic pain.[20 24] Racemic ketamine was first introduced into clinical practice in the 1960s, however, its use in the management of TRD is a much more recent addition to therapy of depression.[20] Early ketamine studies demonstrated rapid, potent reductions in depressive symptoms following the administration of a single sub-anesthetic dose of intravenous racemic ketamine.[30 41] These early findings were groundbreaking, suggesting that ketamine could provide almost immediate relief for individuals unresponsive to conventional treatments. Following ketamine's promising results in treating depression, researchers sought ways to refine its application, aiming to retain its efficacy while minimizing

side effects. Studies indicated that the S-enantiomer, esketamine, was more potent at the NMDA receptor than the R-enantiomer, allowing for therapeutic effects at lower doses.[39] This made esketamine an attractive candidate for development as a more targeted treatment for depression, particularly in patients with TRD. Esketamine was eventually formulated as an intranasal spray, offering a more practical administration route compared to intravenous ketamine, which requires clinical settings for safe administration. The intranasal form also allowed for easier dose control and more accessible outpatient use, reducing the logistical challenges associated with IV infusions.[17]

## ADMINISTRATION

The administration of ketamine and esketamine for treatment-resistant depression (TRD) is an area of active exploration, with multiple delivery routes being studied to maximize efficacy and accessibility. Tested routes for clinical use include intravenous (IV)[27], intranasal[5], oral[1], subcutaneous[12], and intramuscular[21], each with its own benefits and limitations. However, IV and intranasal administration have the most compelling evidence for efficacy and bioavailability in treatment of TRD.[26] IV administration of racemic ketamine is the most studied and widely used route for TRD, delivering the drug directly into the bloodstream to achieve quick therapeutic effects. The standard dosing regimen involves a subanesthetic dose of 0.5 mg/kg, which typically produces antidepressant effects from 40 minutes to 2 hours, with symptom relief peaking within 24 hours and lasting usually 3-7 days for many patients.[18, 23, 34, 46] However, the IV route requires a controlled clinical environment with medical monitoring to manage potential side effects like dissociation, blood pressure elevation, and nausea. Because of these monitoring requirements, IV ketamine is usually limited to specialized clinics, which can restrict access for some patients. Intranasal esketamine is a significant advancement for TRD treatment, providing a more accessible option for patients who may not have easy access to IV infusions. Esketamine's intranasal formulation was specifically developed to allow for outpatient administration in certified treatment centers, where patients self-administer the spray under medical supervision. The recommended dosing protocol for esketamine begins with twice-weekly doses during the induction phase (typically 4 weeks), followed by weekly or biweekly maintenance doses depending on patient response.[29] Intranasal administration offers a practical alternative to IV, as it avoids the need for venous access and allows for self-administration, though it still requires in-clinic monitoring due to possible dissociative effects and cardiovascular side effects. Esketamine's intranasal route has somewhat lower bioavailability (about 45%) compared to IV administration, leading to a slower onset of effects.[15 43]

## PHARMACOLOGY AND MECHANISMS OF ACTION

Both ketamine and esketamine primarily act as antagonists at the NMDA receptor. By inhibiting NMDA receptors, ketamine disrupts normal excitatory signaling, leading to a temporary increase in extracellular glutamate,[13] which, in turn, activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (also known as AMPA receptors) and initiates intracellular signaling pathways that promote synaptogenesis and neuroplasticity. By activating the brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR), ketamine and esketamine help to restore synaptic connections in mood-relevant brain regions, addressing the neurobiological underpinnings of depression.[16 45] BDNF is a crucial mediator of neural plasticity, which involves changes in the structure and function of synapses to enhance resilience against stress-related damage. Traditional antidepressants, by contrast, gradually increase BDNF levels over several weeks, while ketamine activates BDNF release much more rapidly. This rapid activation of BDNF is crucial for its fast-acting antidepressant effects, contributing to the rapid formation of new synaptic connections in mood-regulating brain regions.[2] Signaling of mTOR, when upregulated by ketamine's action, increases protein synthesis and contributes to neural growth, neurogenesis, and the stabilization of synaptic connections.[16] Ketamine's antidepressant effects are further supported by its impact on intracellular pathways and glycogen synthase kinase-3 (GSK-3) inhibition. By inhibiting GSK-3, ketamine enhances neuroplasticity and synaptic resilience, which helps stabilize mood in depressive states. GSK-3 inhibition supports the maintenance of newly formed synapses, adding another layer to ketamine's rapid neurogenic effects.[3] Esketamine binds more strongly to NMDA receptors than racemic ketamine, allowing for lower doses to achieve therapeutic effects. Racemic ketamine, which contains equal parts S- and R-enantiomers, is associated with both antidepressant effects and side effects like dissociation due to its broader receptor activity profile.[39] The elimination half-lives are approximately 5 hours for esketamine and 2–4 hours for racemic ketamine.[47]

## TREATMENT EFFECTS

Clinical trials have consistently demonstrated ketamine's effectiveness in alleviating depressive symptoms in patients with TRD, with most studies focusing on intravenous (IV) racemic ketamine and intranasal esketamine. In comparative studies, ketamine has consistently demonstrated superior response and

remission rates in TRD patients over the short term compared to placebo and traditional antidepressants.[19 25 35] Research indicates that ketamine's rapid effects are partly due to its impact on neuroplasticity, which is particularly valuable for patients with TRD, as it helps repair and strengthen mood-regulating neural circuits that are often compromised in chronic depression. The changes induced by ketamine can, therefore, contribute to a broader, more robust improvement in depressive symptoms, allowing patients to experience relief even in cases where previous treatments have been ineffective.[28] Additionally, racemic ketamine has shown potential as an augmentation strategy, effectively complementing existing antidepressants and cognitive-behavioral therapy to improve outcomes in patients with partial responses to conventional therapies.[14 42] One of ketamine's most compelling treatment effects is its ability to rapidly reduce suicidal ideation, even within a single day of administration. This effect, which can persist for up to a week, is partly independent of ketamine's general antidepressant properties. Studies also indicate that reduction in suicidal ideation can last for up to 6 weeks in people receiving repeat-dose intravenous racemic infusion (0.5 mg/kg). This rapid mechanism can be crucial in managing psychiatric emergencies. [10, 33]

## LIMITATIONS, SIDE EFFECTS AND SAFETY CONCERNS

One of the limitations is the overall duration of the effects. They tend to be short-lived, often lasting between several days to one week, necessitating repeated dosing or maintenance therapy to sustain improvement. Some patients report sustained benefits even with once-weekly or biweekly dosing, though this varies significantly across individuals. Another significant limitation of ketamine and esketamine is the relative lack of long-term safety and efficacy data. While short-term studies have demonstrated ketamine's rapid antidepressant effects, the potential impacts of long-term ketamine use remain unclear. The primary side effects associated with ketamine and esketamine include dissociation, characterized by symptoms such as depersonalization and perceptual disturbances, which typically peak within the first hour post-administration and subside within a few hours. Additionally, psychotomimetic effects, like mild hallucinations, can occur, though they are less common. While some patients tolerate these effects, others may find them distressing, especially in outpatient settings where immediate support may not be available.[38] Although these cognitive effects are generally transient, the potential for long-term impact with repeated or prolonged use remains under investigation. Cardiovascular effects, such as transient increases in blood pressure and heart rate, are another safety concern, particularly for patients with pre-existing hypertension or cardiovascular disease.[41] These effects tend to resolve within hours but warrant careful monitoring during treatment. While controlled medical use at therapeutic doses has not shown a significant increase in substance use disorder risk, the potential for misuse and dependence persists. Recreational ketamine use has been associated with tolerance and dependency, leading to psychological and physical addiction.[8] Although the risk is lower in clinical settings due to strict dosing and monitoring, caution and patient education remain essential to mitigate misuse. The development of esketamine with an intranasal formulation and a more controlled administration route reduces misuse risk, but vigilance is still necessary, especially among individuals with a history of substance use disorders.

*Comparison of ketamine, esketamine and traditional treatment options* [6 7 11 26 32 36 44]

| Parameter | Ketamine (IV) | Esketamine (Intranasal) | Standard Antidepressants (SSRIs/SNRIs) | Augmentation Strategies (e.g., Lithium, Atypical Antipsychotics) |
|---|---|---|---|---|
| Onset of Antidepressant Effect | 40 mins to 2 hrs | 1-2 hrs | 4-8 weeks | Varies depending on combination, typically weeks |
| Peak Efficacy Time | Within 24 hours, effect lasts 3-7 days | Within 24 hours, effect lasts 3-5 days | Weeks to months with continuous treatment | Weeks; may enhance efficacy in partial responders |
| Response Rate in TRD | 70-80% within 24 hrs | 40-60% within 24 hrs | 40-50% after several weeks | Improves response in partial responders |

| | | | | |
|---|---|---|---|---|
| Remission Rate | 50-60% | 30-40% | 25-40% | Enhances remission rates when added to antidepressants |
| Reduction in Suicidal Ideation | 50-60% reduction within hours | 30-40% reduction within hours | Minimal, usually delayed | Supportive effect when combined with antidepressants |
| Discontinuation Due to Side Effects | ~5% for single low dose | 10-15% | 5-20% depending on drug tolerance | 15-25%, based on tolerability of adjunct medications |
| Long-Term Efficacy | Limited data, efficacy decreases with time | Variable, some efficacy up to 6 months | High with consistent use | Effective when continued alongside antidepressant therapy |
| Administration Frequency | 1x weekly or biweekly (maintenance) | Twice-weekly (induction), weekly maintenance | Daily | Dependent on therapy, often daily or as per need |
| Bioavailability | 100% (IV route) | ~45% (intranasal route) | Varies (50-90% for SSRIs, 40-80% for SNRIs) | Dependent on individual drug and route of administration |
| Neuroplasticity Effects | Strong activation of BDNF and mTOR pathways | Moderate neuroplasticity via AMPA | Delayed, usually requires weeks | Augments neuroplastic effects of primary antidepressant |

## CONCLUSIONS

Ketamine and esketamine present promising alternatives for treating treatment-resistant depression (TRD) which affects a substantial number of individuals who do not respond to conventional antidepressants. The rapid response to treatment is especially beneficial for patients in crisis, including those with acute suicidal ideation. The primary administration methods—intravenous (IV) ketamine and intranasal esketamine —expand options for TRD treatment, providing flexibility for patients and clinicians. However, more data is needed and continued research is necessary to assess the long-term safety and efficacy of ketamine-based therapies. Overall, ketamine and esketamine represent significant advancements in the treatment of TRD, providing a faster-acting alternative to traditional antidepressants and offering hope for patients unresponsive to existing therapies.

## REFERENCES

1. Arabzadeh, S., Hakkikazazi, E., Shahmansouri, N., Tafakhori, A., Ghajar, A., Jafarinia, M., & Akhondzadeh, S. (2018). Does oral administration of ketamine accelerate response to treatment in major depressive disorder? Results of a double-blind controlled trial. *Journal of Affective Disorders*, *235*, 236–241. DOI: 10.1016/j.jad.2018.02.056
2. Autry, A. E., Adachi, M., Nosyreva, E., Na, E. S., Los, M. F., Cheng, P., Kavalali, E. T., & Monteggia, L. M. (2011). NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*, *475*(7354), 91–95. https://doi.org/10.1038/nature10130
3. Beurel, E., Song, L., & Jope, R. S. (2011). Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. *Molecular Psychiatry*, *16*(11), 1068–1070. DOI: 10.1038/mp.2011.47
4. Caddy, C., Giaroli, G., White, T. P., Shergill, S. S., & Tracy, D. K. (2014). Ketamine as the prototype glutamatergic antidepressant: Pharmacodynamic actions, and a systematic review and meta-analysis of efficacy. *Therapeutic Advances in Psychopharmacology*, *4*(2), 75–99. DOI:

10.1177/2045125313507739

5. Canuso, C. M., Singh, J. B., Fedgchin, M., Alphs, L., Lane, R., Lim, P., Pinter, C., Hough, D., Sanacora, G., Manji, H., & Drevets, W. C. (2018). Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. *The American Journal of Psychiatry*, *175*(7), 620–630. DOI: 10.1176/appi.ajp.2018.17060720
6. Capuzzi, E., Caldiroli, A., Capellazzi, M., Tagliabue, I., Marcatili, M., Colmegna, F., Clerici, M., Buoli, M., & Dakanalis, A. (2021). Long-Term Efficacy of Intranasal Esketamine in Treatment-Resistant Major Depression: A Systematic Review. *International Journal of Molecular Sciences*, *22*(17), Article 17. DOI: 10.3390/ijms22179338
7. Corriger, A., & Pickering, G. (2019). Ketamine and depression: A narrative review. *Drug Design, Development and Therapy*, *13*, 3051–3067. DOI: 10.2147/DDDT.S221437
8. 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. DOI: 10.1111/nyas.12646
9. Dodd, S., Bauer, M., Carvalho, A. F., Eyre, H., Fava, M., Kasper, S., Kennedy, S. H., Khoo, J.-P., Lopez Jaramillo, C., Malhi, G. S., McIntyre, R. S., Mitchell, P. B., Castro, A. M. P., Ratheesh, A., Severus, E., Suppes, T., Trivedi, M. H., Thase, M. E., Yatham, L. N., … Berk, M. (2021). A clinical approach to treatment resistance in depressed patients: What to do when the usual treatments don't work well enough? *The World Journal of Biological Psychiatry*, *22*(7), 483–494. DOI: 10.1080/15622975.2020.1851052
10. Domany, Y., Shelton, R. C., & McCullumsmith, C. B. (2020). Ketamine for acute suicidal ideation. An emergency department intervention: A randomized, double-blind, placebo-controlled, proof-of-concept trial. *Depression and Anxiety*, *37*(3), 224–233. DOI:10.1002/da.22975
11. Gass, N., Becker, R., Reinwald, J., Cosa-Linan, A., Sack, M., Weber-Fahr, W., Vollmayr, B., & Sartorius, A. (2019). Differences between ketamine's short-term and long-term effects on brain circuitry in depression. *Translational Psychiatry*, *9*(1), 1–11. DOI:10.1038/s41398-019-0506-6
12. George, D., Gálvez, V., Martin, D., Kumar, D., Leyden, J., Hadzi-Pavlovic, D., Harper, S., Brodaty, H., Glue, P., Taylor, R., Mitchell, P. B., & Loo, C. K. (2017). Pilot Randomized Controlled Trial of Titrated Subcutaneous Ketamine in Older Patients with Treatment-Resistant Depression. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *25*(11), 1199–1209. DOI: 10.1016/j.jagp.2017.06.007
13. Gilbert, J. R., & Zarate, C. A. (2020). Electrophysiological biomarkers of antidepressant response to ketamine in treatment-resistant depression: Gamma power and long-term potentiation. *Pharmacology, Biochemistry, and Behavior*, *189*, 172856. DOI: 10.1016/j.pbb.2020.172856
14. Ionescu, D. F., Bentley, K. H., Eikermann, M., Taylor, N., Akeju, O., Swee, M. B., Pavone, K. J., Petrie, S. R., Dording, C., Mischoulon, D., Alpert, J. E., Brown, E. N., Baer, L., Nock, M. K., Fava, M., & Cusin, C. (2019). Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: A randomized, double blind, placebo controlled trial. *Journal of Affective Disorders*, *243*, 516–524. DOI: 10.1016/j.jad.2018.09.037
15. Jonkman, K., Duma, A., Olofsen, E., Henthorn, T., van Velzen, M., Mooren, R., Siebers, L., van den Beukel, J., Aarts, L., Niesters, M., & Dahan, A. (2017). Pharmacokinetics and Bioavailability of Inhaled Esketamine in Healthy Volunteers. *Anesthesiology*, *127*(4), 675–683. DOI: 10.1097/ALN.0000000000001798
16. K V, A., Mohan, A. S., & Chakravarty, S. (2020). Rapid acting antidepressants in the mTOR pathway: Current evidence. *Brain Research Bulletin*, *163*, 170–177. DOI: 10.1016/j.brainresbull.2020.07.022
17. Kim, J., Farchione, T., Potter, A., Chen, Q., & Temple, R. (2019). Esketamine for Treatment-Resistant Depression—First FDA-Approved Antidepressant in a New Class. *The New England Journal of Medicine*, *381*(1), 1–4. DOI: 10.1056/NEJMp1903305
18. Kishimoto, T., Chawla, J. M., Hagi, K., Zarate, C. A., Kane, J. M., Bauer, M., & Correll, C. U. (2016). Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: A meta-analysis of efficacy, safety and time trajectories. *Psychological Medicine*, *46*(7), 1459–1472. DOI: 10.1017/S0033291716000064
19. Kryst, J., Kawalec, P., Mitoraj, A. M., Pilc, A., Lasoń, W., & Brzostek, T. (2020). Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: A meta-analysis of randomized clinical trials. *Pharmacological Reports: PR*, *72*(3), 543–562. DOI: 10.1007/s43440-020-00097-z
20. Li, L., & Vlisides, P. E. (2016). Ketamine: 50 Years of Modulating the Mind. *Frontiers in Human Neuroscience*, *10*, 612. DOI: 10.3389/fnhum.2016.00612
21. Loo, C. K., Gálvez, V., O'Keefe, E., Mitchell, P. B., Hadzi-Pavlovic, D., Leyden, J., Harper, S., Somogyi,

A. A., Lai, R., Weickert, C. S., & Glue, P. (2016). Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatrica Scandinavica*, *134*(1), 48–56. DOI: 10.1111/acps.12572

22. Madsen, K. B., Momen, N. C., Petersen, L. V., Plana-Ripoll, O., Haarman, B. C. M., Drexhage, H., Mortensen, P. B., McGrath, J. J., & Munk-Olsen, T. (2021). Bidirectional associations between treatment-resistant depression and general medical conditions. *European Neuropsychopharmacology*, *51*, 7–19. DOI: 10.1016/j.euroneuro.2021.04.021
23. Marcus, M., Yasamy, M. T., van Ommeren, M. van, Chisholm, D., & Saxena, S. (2012). *Depression: A Global Public Health Concern*. https://doi.org/10.1037/e517532013-004
24. Mathew, S. J., Shah, A., Lapidus, K., Clark, C., Jarun, N., Ostermeyer, B., & Murrough, J. W. (2012). Ketamine for treatment-resistant unipolar depression: Current evidence. *CNS Drugs*, *26*(3), 189–204. DOI: 10.2165/11599770-000000000-00000
25. McIntyre, R. S., Carvalho, I. P., Lui, L. M. W., Majeed, A., Masand, P. S., Gill, H., Rodrigues, N. B., Lipsitz, O., Coles, A. C., Lee, Y., Tamura, J. K., Iacobucci, M., Phan, L., Nasri, F., Singhal, N., Wong, E. R., Subramaniapillai, M., Mansur, R., Ho, R., … Rosenblat, J. D. (2020). The effect of intravenous, intranasal, and oral ketamine in mood disorders: A meta-analysis. *Journal of Affective Disorders*, *276*, 576–584. DOI: 10.1016/j.jad.2020.06.050
26. McIntyre, R. S., Rosenblat, J. D., Nemeroff, C. B., Sanacora, G., Murrough, J. W., Berk, M., Brietzke, E., Dodd, S., Gorwood, P., Ho, R., Iosifescu, D. V., Lopez Jaramillo, C., Kasper, S., Kratiuk, K., Lee, J. G., Lee, Y., Lui, L. M. W., Mansur, R. B., Papakostas, G. I., … Stahl, S. (2021). Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. *The American Journal of Psychiatry*, *178*(5), 383–399. DOI: 10.1176/appi.ajp.2020.20081251
27. Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., Iqbal, S., Pillemer, S., Foulkes, A., Shah, A., Charney, D. S., & Mathew, S. J. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. *The American Journal of Psychiatry*, *170*(10), 1134–1142. DOI: 10.1176/appi.ajp.2013.13030392
28. Murrough, J. W., Wan, L.-B., Iacoviello, B., Collins, K. A., Solon, C., Glicksberg, B., Perez, A. M., Mathew, S. J., Charney, D. S., Iosifescu, D. V., & Burdick, K. E. (2014). Neurocognitive effects of ketamine in treatment-resistant major depression: Association with antidepressant response. *Psychopharmacology*, *231*(3), 481–488. DOI: 10.1007/s00213-013-3255-x
29. Nijs, M., Wajs, E., Aluisio, L., Turkoz, I., Daly, E., Janik, A., Borentain, S., Singh, J. B., DiBernardo, A., & Wiegand, F. (2020). Managing Esketamine Treatment Frequency Toward Successful Outcomes: Analysis of Phase 3 Data. *International Journal of Neuropsychopharmacology*, *23*(7), 426–433. https://doi.org/10.1093/ijnp/pyaa027
30. Oye, I., Paulsen, O., & Maurset, A. (1992). Effects of ketamine on sensory perception: Evidence for a role of N-methyl-D-aspartate receptors. *The Journal of Pharmacology and Experimental Therapeutics*, *260*(3), 1209–1213.
31. Papakostas, G. I., & Ionescu, D. F. (2015). Towards new mechanisms: An update on therapeutics for treatment-resistant major depressive disorder. *Molecular Psychiatry*, *20*(10), 1142–1150. DOI: 10.1038/mp.2015.92
32. Parker, G., Ricciardi, T., & Hadzi-Pavlovic, D. (2020). Placebo response rates in trials of antidepressant drugs in adults with clinical depression: Increasing, decreasing, constant or all of the above? *Journal of Affective Disorders*, *271*, 139–144. DOI: 10.1016/j.jad.2020.03.065
33. Phillips, J. L., Norris, S., Talbot, J., Hatchard, T., Ortiz, A., Birmingham, M., Owoeye, O., Batten, L. A., & Blier, P. (2020). Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *45*(4), 606–612. DOI: 10.1038/s41386-019-0570-x
34. Romeo, B., Choucha, W., Fossati, P., & Rotge, J.-Y. (2015). Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. *Psychiatry Research*, *230*(2), 682–688. DOI: 10.1016/j.psychres.2015.10.032
35. Sanacora, G., Frye, M. A., McDonald, W., Mathew, S. J., Turner, M. S., Schatzberg, A. F., Summergrad, P., Nemeroff, C. B., & American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. (2017). A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. *JAMA Psychiatry*, *74*(4), 399–405. DOI: 10.1001/jamapsychiatry.2017.0080
36. Schwartz, J., Murrough, J. W., & Iosifescu, D. V. (2016). Ketamine for treatment-resistant depression: Recent developments and clinical applications. *Evidence-Based Mental Health*, *19*(2), 35–38. DOI: 10.1136/eb-2016-102355
37. Shah, A. A. (2016). Novel Approaches for Managing Treatment-Resistant Depression. *Psychiatric*

*Annals*, *46*(4), 220–222. DOI:10.3928/00485713-20160229-01

38. Short, B., Fong, J., Galvez, V., Shelker, W., & Loo, C. K. (2018). Side-effects associated with ketamine use in depression: A systematic review. *The Lancet. Psychiatry*, *5*(1), 65–78. https://doi.org/10.1016/S2215-0366(17)30272-9
39. Swainson, J., Thomas, R. K., Archer, S., Chrenek, C., MacKay, M.-A., Baker, G., Dursun, S., Klassen, L. J., Chokka, P., & Demas, M. L. (2019). Esketamine for treatment resistant depression. *Expert Review of Neurotherapeutics*, *19*(10), 899–911. DOI: 10.1080/14737175.2019.1640604
40. Tundo, A., Filippis, R. de, & Proietti, L. (2015). Pharmacologic approaches to treatment resistant depression: Evidences and personal experience. *World Journal of Psychiatry*, *5*(3), 330. DOI: 10.5498/wjp.v5.i3.330
41. Wan, L.-B., Levitch, C. F., Perez, A. M., Brallier, J. W., Iosifescu, D. V., Chang, L. C., Foulkes, A., Mathew, S. J., Charney, D. S., & Murrough, J. W. (2015). Ketamine safety and tolerability in clinical trials for treatment-resistant depression. *The Journal of Clinical Psychiatry*, *76*(3), 247–252. DOI: 10.4088/JCP.13m08852
42. Wilkinson, S. T., Rhee, T. G., Joormann, J., Webler, R., Ortiz Lopez, M., Kitay, B., Fasula, M., Elder, C., Fenton, L., & Sanacora, G. (2021). Cognitive Behavioral Therapy to Sustain the Antidepressant Effects of Ketamine in Treatment-Resistant Depression: A Randomized Clinical Trial. *Psychotherapy and Psychosomatics*, *90*(5), 318–327. DOI: 10.1159/000517074
43. Yanagihara, Y., Ohtani, M., Kariya, S., Uchino, K., Hiraishi, T., Ashizawa, N., Aoyama, T., Yamamura, Y., Yamada, Y., & Iga, T. (2003). Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. *Biopharmaceutics & Drug Disposition*, *24*(1), 37–43. DOI: 10.1002/bdd.336
44. Yavi, M., Lee, H., Henter, I. D., Park, L. T., & Zarate, C. A. (2022). Ketamine treatment for depression: A review. *Discover Mental Health*, *2*(1), 9. DOI: 10.1007/s44192-022-00012-3
45. Zanos, P., & Gould, T. D. (2018). Mechanisms of ketamine action as an antidepressant. *Molecular Psychiatry*, *23*(4), 801–811. DOI: 10.1038/mp.2017.255
46. Zarate, C. A., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., Charney, D. S., & Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*, *63*(8), 856–864. DOI: 10.1001/archpsyc.63.8.856
47. Zhao, X., Venkata, S. L. V., Moaddel, R., Luckenbaugh, D. A., Brutsche, N. E., Ibrahim, L., Zarate, C. A., Mager, D. E., & Wainer, I. W. (2012). Simultaneous population pharmacokinetic modelling of ketamine and three major metabolites in patients with treatment-resistant bipolar depression. *British Journal of Clinical Pharmacology*, *74*(2), 304–314. DOI: 10.1111/j.1365-2125.2012.04198.x

back