Global Journal of Medicine & Public Health

Ketamine for Treatment-Resistant Depression: A Systematic Review

Farnaz Shaygan Majd [1], Somaieh Salehi[2], Zahra Rezaie[3]*

ABSTRACT

Ketamine has attracted considerable attention as a novel treatment for depression due to its rapid and potent antidepressant effect. On the one hand, this drug has attracted the attention of specialists treating treatment-resistant depressive disorders as an alternative drug for therapeutic methods such as electroconvulsive therapy (ECT), and on the other hand, due to its properties and positive therapeutic performance in preventing suicide and side effects. Low cognition and the possibility of a faster effect and a good durability of the therapeutic effects, especially in the case of repeated ketamine injections, are of interest. Therefore, we reviewed and discussed the mechanism of ketamine's effect and its performance in treatment-resistant depression, as well as the positive points and side effects of Ketamine.

Methodology

A computerized search of the databases was conducted between January 2014 and September 2024 using the following keywords, including "Depression", "Ketamine" and "Treatment-resistant Depression".

Results

After applying inclusion and exclusion criteria and appraising the quality, eight studies were included and the data were extracted. Some of the articles reported the rapid antidepressant effects of ketamine. Few studies represented long-term effects and only one study showed no effectiveness of this treatment.

Conclusion

Ketamine represents a significant advancement in managing TRD, demonstrating rapid effects and potential improvements in mood and cognitive function. However, the necessity for repeated treatments and ongoing research into long-term effects and safety remains critical to fully understanding its role in depression management.

Keywords: Ketamine; S-ketamine; Treatment-Resistant Depression

GJMEDPH 2025; Vol. 14, issue 3 | OPEN ACCESS

2*Corresponding author: Somaieh Salehi, Assistant Professor in Department of Psychology and Counseling, Faculty of Psychology and Educational Sciences, Islamic Azad University, South Tehran Branch, Tehran, Iran,ORCID: https://orcid.org/0000-0003-2749-9633,Email: 2dr.salehi@gmail.com, Tel: (+98) 9126076770; 1.Farnaz Shaygan Majd, M.S in Clinical Psychology, Department of Psychology and Counseling, Faculty of Psychology and Educational sciences, Islamic Azad University, South Tehran Branch, Tehran, Iran, ORCID: https://orcid.org/0009-0004-1364-3731,Email: shayganmajdfarnaz@gmail.com, Tel: (+98) 9358290886; 3. Zahra Rezaie, M.S in Family Counseling, Department of Psychology and Counseling, Faculty of Psychology and Educational sciences, Islamic Azad University, South Tehran Branch, Tehran, Iran,ORCID: https://orcid.org/0009-0008-7499-6409,Email: zhrar846@gmail.com, Tel: (+98) 9193087136

Conflict of Interest—none | Funding—none

INTRODUCTION

Major depressive disorder (MDD) is a chronic and highly prevalent disorder associated with significant economic costs and disability globally (1). The global prevalence of MDD is estimated at 4% and approximately 322 million people live with this disorder (2), this disorder is one of the main causes of disability in high-, middle- and low-income countries (2). Treatment-resistant depression (TRD) is associated with greater physical comorbidity, substance abuse, and excess mortality, including through suicide (3). On the other hand, despite the significant increase in treatment options for treating patients with major depressive disorder, one third of these patients do not respond satisfactorily to antidepressant treatments (4). even more so with bipolar disorder (4). Patients who do not respond adequately to at least 2 treatments are usually labeled as treatment-resistant depression (5). On the other hand, 40 to 60% of MDD patients also have anxiety symptoms. This makes scientists look for more effective treatments to help depressed and anxious patients (6).

Currently, antidepressants that target the monoamine system produce modest improvements in depressive symptoms for many people with MDD (5). Studies have shown that approximately 35% of people with depression experience complete recovery, while 65% are still symptomatic after multiple trials of antidepressants (5) significantly longer and experience more work-related disorders. Until recently, approved antidepressants mainly targeted the brain's monoamine systems (i.e., those involving serotonin, dopamine, norepinephrine) (7). Monoaminergic antidepressants are slow-acting and require adaptation, and in many cases are either not tolerated or are insufficient to produce symptomatic relief. The delayed therapeutic benefit of monoaminergic antidepressants is associated with slow increases in neurogenesis (especially in the hippocampus) and transcriptional changes that reconfigure neural circuits (8). The limited targeting and slow response rate of conventional antidepressants are incentives for new pharmacological approaches. In this way, the current first-line antidepressants are only average, and the current treatments, including ECT, have advantages and disadvantages, which makes specialists always look for ways with fewer side effects and better results (8).

An emerging method in the treatment of TRD is the use of subanesthetic doses of ketamine (9-11). Ketamine is a racemic mixture of two enantiomers of R- and Es-ketamine (12-15). Ketamine is an anesthetic and analgesic agent that shows antidepressant effect in major depression. Ketamine is a new treatment due to its rapid and strong antidepressant effect. For depression, a preliminary proof-of-concept study with ketamine showed that a single, intravenous dose of the drug has a rapid and sustained antidepressant effect in major depression (12). Subsequent basic research and clinical trials have confirmed that ketamine is effective for patients with TRD (6, 9, 16, 17) and, separately, reduced the severity of suicidal ideation in patients with TRD (4, 18).

As mentioned, due to the not very favorable response of patients with TRD to the usual treatments of this disease, specialists in this field are always looking for newer and more efficient ways to treat these patients. Ketamine is one of the suggested ways to treat these patients. Since the beginning of the treatment of patients with this drug, numerous and different opinions have been raised regarding the characteristics and functional level of this drug and its possible side effects, which has created the need to examine these different views in the form of a review study. Key findings of previous studies suggest that ketamine may offer rapid antidepressant effects, ketamine's psychoactive effects and therapeutic benefits, though these may be less durable compared to other treatments like electroconvulsive therapy (ECT). According to previous review studies there is high heterogeneity regarding the effects of ketamine among TRD patients. Therefore, the purpose of this article is to review some of the studies conducted in this field and collect and categorize these views as much as possible and according to the existing limitations based on efficacy, mechanism of action, long term effect and clinical implications.

Materials and Methods

A comprehensive review of a diverse range of scientific sources was undertaken to ensure a thorough understanding of the research landscape.

ISSN# 2277-9604

The researcher systematically searched for relevant scientific articles published in various fields related to the study. This search was conducted across multiple reputable databases, including EMBASE, Scopus, and Medline (via PubMed), which are known for their extensive collections of peer-reviewed literature. Additionally, Google Scholar was utilized for its broad access to scholarly articles, while ProQuest provided valuable multidisciplinary resources, and Cochrane focused on systematic reviews in healthcare. The database of the SID University Jihad Scientific Information Center was also accessed, offering important regional insights and research outputs. By leveraging these diverse sources, we aimed to capture a wide spectrum of findings and perspectives, thereby enhancing the robustness and credibility of our analysis.

Inclusion and exclusion criteria

Inclusion criterion for data source is research carried out on ketamine therapy on patients diagnosed with treatment-resistant depression, main research output will be depression rate reductions, depression rate, suicidal thoughts, research are published in English, published within recent 10 years (2014-2024) in form of full article, and research that uses randomized controlled trial.

Exclusion criteria are research that only consists of abstract, case control, control study, cohort study, review articles and study with an intervention such as traditional pharmacology and brain stimulus therapy.In this search, articles were searched with the keyword's treatment-resistant depression, ketamine, treatments for treatment-resistant depression, and TRD. As a result of this search, about 65 articles were found, of which 18 articles were selected for review after content analysis. Finally, 8 articles included for the details content analysis for the review study. It should be noted that all of these articles are in English and have been published in reputable scientific journals, and all of them have been published in the period of 2014 and beyond (Figure 1).

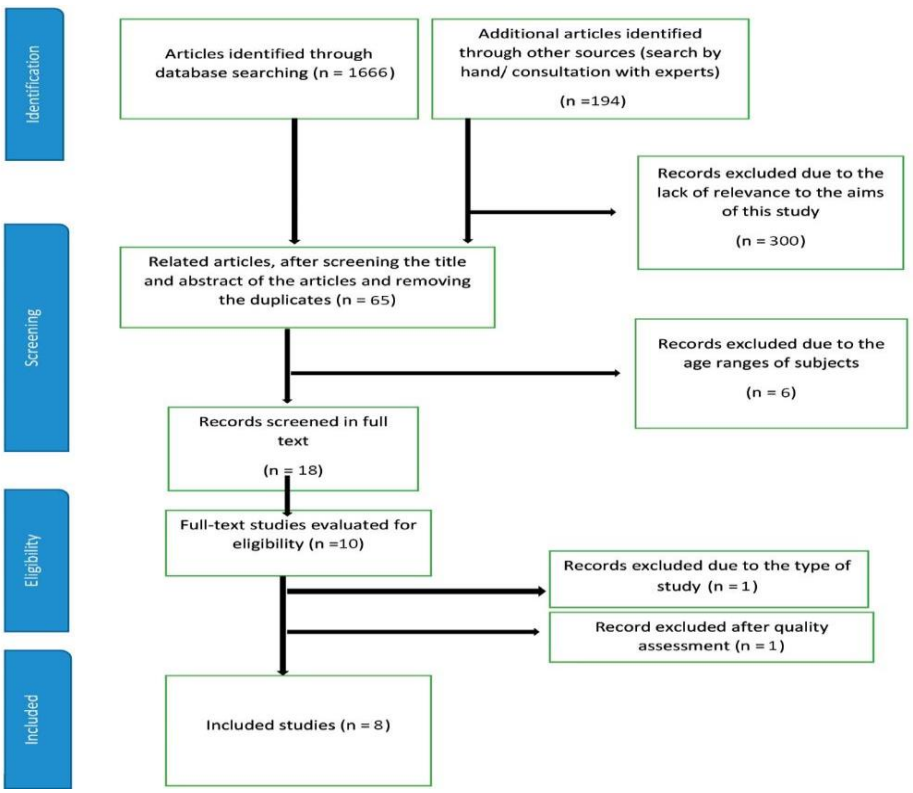

Figure 1. Study selection flew

Study selection and eligibility criteria

Articles collected was organized by using Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Identification, screening, eligibility, and include will be carried out to include or exclude articles collected as shown in Figure 1. It is essential to disclose any potential conflicts of interest, and to ensure the integrity of the review process, two independent reviewers conducted the data extraction and quality assessment, thereby enhancing the reliability of the findings.

Results

This review included eight studies (Table 1). These articles study the effect of ketamine in treating depression and its associated symptoms. According to the PRISMA diagram, here's a table summarizing the key points from the results section: Relevance focused on findings that specifically relate to the effectiveness of ketamine in treating depression and associated symptoms, particularly in treatment-resistant depression (TRD). Key themes are grouped similar findings together, such as: efficacy of ketamine in reducing depressive symptoms, impact on suicidal thoughts, mechanisms of action (e.g., NMDA receptor antagonism), long-term effects and treatment duration. Results section included the authors and publication year for reference, maintaining the original context of the studies. The results aimed to present the information clearly and concisely, avoiding unnecessary details while retaining essential findings. A wide array of research was included, ensuring representation from multiple disciplines and methodologies to offer a holistic perspective on the effects of ketamine. Table 1 shows key findings from all studies (based on inclusion and exclusion criteria) according to the authors, year, country, and key findings related to the efficacy of ketamine in treating depression and its associated symptoms.

Table 1. Characteristics of included articles

The effects of ketamine on TRD	Authors Year Country	Methods	Outcome measured in reducing depressive symptoms	Key Findings
Rapid effects	Brody et al. 2024 US (19)	- Retrospective chart review of inpatients with non-psychotic MDD who received ketamine infusion treatment over a 3-year period - Effectiveness of treatment was assessed using changes in Montgomery Asberg Depression Rating Scale (MADRS) scores, with response defined as a 50% reduction in MADRS and remission defined as MADRS ≤ 10 - Frequency of adverse events was also reported	1. Change in Montgomery Asberg Depression Rating Scale (MADRS) scores 2. Rate of treatment response (defined as 50% reduction in MADRS score) 3. Rate of remission (defined as MADRS score ≤ 10) 4. Frequency of adverse events	1.Forty-one patients suffering from MDD received treatment and had outcome information. Nineteen patients (46.5%) qualified for response, while fifteen patients (26.5%) qualified for remission during the treatment. Four patients (10%) experienced negative psychological or behavioral effects. 2.Racemic ketamine infusion serves as an effective therapy for hospitalized individuals suffering from treatment-resistant major depressive disorder, though adverse effects may arise.

ISSN# 2277-9604

	Peters et al. 2023 US (20)	- Review of medical charts from 30 patients admitted with depression resistant to treatment. Patients were administered a maximum of 4 doses of intranasal racemic ketamine (50 mg or 75 mg) during a 7-day period. - Symptoms of depression were assessed with the Hamilton Depression Rating Scale or the Montgomery-Åsberg Depression Rating Scale. - Suicidal thoughts were evaluated and showed an average reduction of 68.5%.	1. Change in depression symptoms, as measured by the Hamilton Depression Rating Scale or the Montgomery-Åsberg Depression Rating Scale 2. Change in suicidal ideation	Intranasal racemic ketamine was safe and effective in treating depressive symptoms and suicidal ideation in hospitalized patients with treatment-resistant depression.
	Vincenzo et al. 2021 Canada (21)	- Retrospective study design - Evaluation of ketamine monotherapy (n=39) versus ketamine as an adjunctive therapy (n=181) for treatment-resistant depression. - Results assessed through self-reported measures, such as the QIDS-SR16, concerning effects on depression, suicidality, anxiety, and functional impairment. - Performed at one localized clinic in the community - Uncontrolled, non-	The main outcomes assessed in this research were effects on depression, reduction of suicidal tendencies, anxiety relief, and improvement in functional impairment.	1.Ketamine monotherapy significantly reduces suicidal thoughts compared to control groups. Ketamine monotherapy versus adjunctive ketamine in adults with treatment-resistant depression 2.Ketamine monotherapy significantly reduces suicidal thoughts, with a smaller effect size compared to the control group. Repeated intravenous ketamine administration may prolong the rapid reduction in suicidal thoughts.

		randomized, and open-label		
	Fedgchin M et al. 2019 (22)	This Phase 3, double-blind, multicenter trial included adults experiencing moderate-to-severe depression who did not respond to two or more antidepressants during the current episode of depression. Eligible individuals (N = 346) were randomized (1:1:1) to receive nasal spray therapy (esketamine [56 or 84 mg] or placebo) twice a week along with a newly started, open-label, daily oral antidepressant for a duration of 4 weeks. The main efficacy endpoint was the alteration from baseline to day 28 in the total score of the Montgomery-Asberg Depression Rating Scale, assessed by blinded, remote evaluators. According to the established statistical testing order, esketamine 84 mg/antidepressant needed to be significant for the formal testing of es-ketamine 56 mg/antidepressant.	The primary outcome measured was the change from baseline to day 28 in the Montgomery- Asberg Depression Rating Scale (MADRS) total score.	1.The higher 84 mg dose of esketamine did not reach statistical significance, yet the treatment effects for both dosages of esketamine numerically favored the esketamine groups compared to the antidepressant/placebo group. 2.The 56 mg dose of esketamine demonstrated a statistically significant difference compared to the antidepressant/placebo group, indicating possible effectiveness of the lower dosage. 3.Esketamine was shown to be safe and well-tolerated, with no significant differences in safety and tolerability observed between the two doses.
Rapid and sustained effects	Siegel et al. 2021 US (23)	Adult individuals aged 18–65 diagnosed with major depressive disorder were enrolled. A validating clinical evaluation by psychiatrists employed	1)Clinical response, or alteration in depressive symptoms, during an 8-week timeframe after a 96-hour ketamine infusion.	-The prolonged ketamine infusion was mainly well-received by most participants, showing minimal side effects. -The infusion led to a

		the Montgomery-Asberg Depression Rating Scale (MADRS), setting a cutoff score of ≥ 22 for moderate symptom severity. Treatment resistance was defined by an absence of response to at least two trials with antidepressants at suitable dosages and durations. Ongoing use of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors was allowed if the dosage remained unchanged for a minimum of 6 weeks prior to the infusion. Healthy controls were concurrently recruited for imaging studies and paired with depressed individuals according to demographics and imaging quality. The research obtained approval from the institutional review board, and all participants gave informed consent.	2) Alterations in functional connectivity within the brain's limbic system, assessed through resting-state fMRI, prior to and two weeks following the ketamine infusion, in comparison to healthy individuals.	rapid and enduring reduction in depressive symptoms, as indicated by the MADRS scale evaluation. -The infusion led to changes in brain functional connectivity, particularly a decrease in hyperconnectivity in the subequal anterior cingulate cortex and limbic system.
	Phillips et al 2020 USA (24)	- Crossover study design that is randomized and double-blind. - Participants were administered a single injection of either ketamine or midazolam (control). Following relapse, participants underwent 6 open-label ketamine	Reported significant reductions in SI following single and repeated ketamine infusions, with 69% of participants experiencing complete alleviation of SI	One ketamine infusion led to a more significant decrease in suicidal thoughts than the control (midazolam), with the peak effect noted 7 days post-infusion. - Multiple ketamine infusions resulted in cumulative decreases in suicidal thoughts, but maintenance infusions did

		infusions administered 3 times a week over a span of 2 weeks. Responders (with a decrease of ≥50% in MADRS) subsequently underwent 4 extra open-label ketamine infusions administered weekly.		not produce any additional changes. - After undergoing multiple ketamine infusions, 69% of participants reported a total removal of suicidal thoughts.
	Moda-Sava et al (2019) USA (8)	- Two-photon imaging to study dendritic spine remodeling and neuronal activity dynamics in the prefrontal cortex (PFC) under chronic stress and ketamine treatment conditions. - Use of an optogenetic tool to selectively manipulate the survival of newly formed spines after ketamine treatment.	1) Dendritic spine density in prefrontal cortical pyramidal cells 2) Coordinated neuronal activity in prefrontal cortical microcircuits 3) Motivated escape behavior, as a measure of antidepressant effects	The formation of spines in the prefrontal cortex supports the remission of certain depression-related behaviors following ketamine treatment by replenishing lost spines and reestablishing coordinated ensemble activity in microcircuits of the PFC. Pharmacological and neurostimulatory treatments aimed at improving and maintaining the recovery of lost synapses could hence be beneficial for facilitating long-term remission.
No significant effects	Takahash et al. 2021 Japan (25)	This Phase 2b, randomized, double-blind (DB), placebo-controlled trial was carried out in adult Japanese individuals with treatment-resistant depression (TRD) who met the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) criteria for major depressive disorder and had not responded to ≥ 1 but < 5 different antidepressants (ADs) during the current	Change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at Day 28 of the double-blind induction phase	Esketamine did not demonstrate a statistically significant enhancement in depressive symptoms when compared to placebo among Japanese patients with treatment-resistant depression. - Esketamine showed a greater frequency of adverse events in comparison to placebo.

	episode at screening. Patients received a new oral antidepressant for 6 weeks (prospective lead-in phase); those who did not respond were randomized (2:1:1:1) to receive either placebo or esketamine (28-, 56-, or 84-mg) nasal spray along with the ongoing use of the antidepressant for 4 weeks (double-blind induction phase). Responders (≥50% decrease from baseline in the Montgomery-Asberg Depression Rating Scale [MADRS] total score) from the DB induction phase proceeded into the 24-week post treatment phase, and those who experienced a relapse were allowed to join a 4-week open-label (OL) second induction (flexibly-dosed esketamine). The main efficacy endpoint, the difference from baseline in the MADRS total score at Day 28 during the DB induction phase, was determined using a mixed-effects model that utilized repeated measures pairwise comparisons with a Dunnett adjustment.	

This research examines the application of ketamine for managing individuals with TRD (8, 19-23,25,26). It emphasizes the swift antidepressant impact of ke tamine, its ability to lower suicidal thoughts, and the necessity for ongoing treatments to sustain advantages. In terms of efficacy, multiple studies confirm that ketamine provides rapid and sustained antidepressant effects, especially in patients with TRD (19-22). Furthermore, up to 70% of TRD patients may respond positively to ketamine,

ISSN# 2277-9604

with effects observable as soon as four hours post-infusion and peaking at 24 hours. The benefits of ketamine are often short-lived, requiring repeated treatments for sustained efficacy. The other two studies showed rapid and sustained effects (23, 26). However, based on inclusion and exclusion criteria, one study in Japanese individuals showed no efficacy of Ketamine for TRD patients (25).

DISCUSSION

Overall, the studies provide a more nuanced understanding of ketamine's efficacy, its effects on suicidal thoughts, mechanisms of action, long-term benefits, safety, tolerance, and advancements in both research and clinical practice. In terms of ketamine's efficacy, it appears to be a promising rapid-acting treatment alternative for patients who do not respond to conventional antidepressants. Racemic ketamine infusion is an effective therapy for hospitalized individuals suffering from treatment-resistant major depressive disorder, although adverse effects may occur (20). Es-ketamine has been shown to be safe and well-tolerated, with no significant differences in safety and tolerability observed between the two doses (22).Research indicates that ketamine significantly reduces the severity of suicidal thoughts in affected patients (14, 15). Depressed individuals, particularly those with treatment-resistant depression (TRD), often grapple with suicidal thoughts and attempts. This concern prompted researchers to investigate whether ketamine impacts suicidality in these patients while studying its effects on TRD. Results from a study conducted at the Rapid Treatment Center of Excellence in Canada by Di Vincenzo and colleagues revealed that individuals receiving monotherapy with ketamine experienced a significant reduction in suicidal thoughts. The Quick Inventory of Depressive Symptomatology Self-Report 16-item (QIDS-SR16) demonstrated a smaller effect size compared to the control group, with the difference being statistically significant (21). This research suggests that ketamine could be considered a potential emergency strategy for individuals at high risk of suicide, serving as an alternative to hospitalization, which can be more disruptive and costly. However, it remains unclear how long the antidepressant effects of repeated ketamine injections last and whether the reduction in suicidal thoughts induced by ketamine can be sustained with alternative pharmacological strategies.

In terms of its mechanism of action, ketamine functions as an NMDA receptor blocker, a distinctive feature among antidepressants. It activates pathways essential for synaptogenesis and the formation of dendritic spines, contributing to its antidepressant effects. Another study assessed the effects of ketamine and es-ketamine on overall functioning in patients with treatment-resistant depression (TRD), showing improvements in psychosocial functioning. Research indicates that ketamine is effective both as a standalone treatment and as an add-on therapy, demonstrating significant antidepressant effects in both scenarios. Furthermore, studies suggest that ketamine therapy could enhance neuroplasticity, potentially aiding in the development of new treatments for depression. (27).

In terms of long-term relief, some studies suggest that long-term infusions can provide relief for several months (8, 17, 20). While ketamine treatment has been examined from various perspectives, a key question remains: does a single injection provide desirable results, or is repeated administration necessary for greater effectiveness? Phillips and colleagues conducted a study involving forty-one participants with treatment-resistant depression, completing a randomized, double-blind, crossover study that compared single injections of ketamine to midazolam (an active placebo). After experiencing a relapse of depressive symptoms, participants received an open-label course of six ketamine injections administered three times a week. At the end of the study, it was found that, compared to midazolam, a single injection of ketamine produced a significantly greater reduction in depressive symptoms at the primary efficacy endpoint (24 hours after infusion). Mixed linear models indicated cumulative antidepressant effects, meaning that repeated injections doubled the rate of antidepressant response. Fifty-nine percent of participants met response criteria after repeated injections, with an average of three injections needed to achieve this response. The study concluded that repeated ketamine injections have cumulative and sustained antidepressant effects,

ISSN# 2277-9604

maintaining a reduction in depressive symptoms among responders (26). In a study conducted by Joshua Siegel and colleagues at the University Of Chicago School Of Medicine, ketamine was identified as an antagonist of the NMDA subtype of the glutamate receptor, making it unique among antidepressants. A short 40-minute ketamine injection often provides relief for patients who have not responded to treatments targeting biogenic amines. The clinical response to ketamine injections typically manifests within a few hours, although the duration of the drug's antidepressant effects in the body lasts about one week. Clinical trials of ketamine for chronic pain have reported that long-term administration over 4 to 14 days can provide sustained symptom relief for up to 8 months (17).

Regarding safety and tolerance, evaluations indicated that the majority of participants did not show significant alterations in vital signs during ketamine infusions; however, a few did report increased blood pressure. The results suggest that ketamine is generally well-tolerated, emphasizing the need for further research to examine its safety in diverse populations, such as older adults. Ketamine treatment may lead to issues like ketamine-induced cystitis, which requires prompt identification and cessation of treatment for symptom relief.

Limitation

This study encountered several limitations. Firstly, while there was an overall prevalence of ketamine use for treatment-resistant depression reported in various studies, there was limited information regarding the sample sizes of each subgroup and the number of individuals receiving ketamine treatment within those subgroups. This lack of data hindered some subgroup analyses. Secondly, the included studies did not consider factors associated with ketamine treatment for depression, such as socioeconomic status, which meant that prevalence could not be analyzed in relation to these factors. Lastly, prevalence studies on ketamine for treatment-resistant depression were not available for every region in Iran. Therefore, it is suggested that future research should address these issues by employing precise diagnostic criteria, ensuring adequate sample sizes, and providing detailed results for subgroups to yield a more thorough understanding of the prevalence of ketamine for treatment-resistant depression in Iran.

Conclusion

This research emphasizes the necessity for further investigations to comprehend the long-term effects and mechanisms of ketamine therapy. The study highlights the promise of ketamine as a fast-acting option for treatment-resistant depression (TRD), demonstrating positive impacts on cognitive abilities and overall psychosocial outcomes. Furthermore, more research is needed to determine whether the reduction in suicidal thoughts following ketamine treatment definitively leads to a decreased risk of suicidal behavior and attempts. Additional studies are required to comprehensively understand the lasting effects and optimal treatment guidelines for ketamine therapy in clinical settings.

REFERENCES

1. Marx W, Penninx B, Solmi M, Furukawa TA, Firth J, Carvalho AF, et al. Major depressive disorder. Nat Rev Dis Primers. 2023;9(1):44.
2. Organization WH. World Health Organization. Depressive Disorder (Depression) Geneva, Switzerland: World Health Organization; 2024 [Available from: https://www.who.int/news-room/fact-sheets/detail/depression.
3. Conway CR, George M.S, Sackeim HA. Toward an evidence-based, operational definition of treatment-resistant depression: when enough is enough. JAMA psychiatry. 2017;74(1):9-10.
4. Singh B, Vande Voort JL, Pazdernik VK, Frye MA, S. K. Treatment-resistant depression patients with baseline suicidal ideation required more treatments to achieve therapeutic response with ketamine/esketamine.2024; j.jad.351 :534–540. jjad. 2024; 351:534-40.
5. Vestring S, Galuba V, Kern E, Voita S, Berens F, Nasiri D, et al. Ketamine in multiple treatment-resistant depressed inpatients: A naturalistic cohort study. J Affect Disord. 2024;1(350):895-9.
6. Włodarczyk A, Słupski J, Szarmach J, WJ. C. Single arketamine in treatment resistant depression: Presentation of 3 cases with regard to sick-leave duration. .96:104016. AJP. 2024;96(104016).
7. Dunlop BW, Rajendra JK, Craighead WE, Kelley ME, McGrath CL, Choi KS, et al. Functional connectivity of the subcallosal cingulate cortex and differential outcomes to treatment with cognitive-behavioral therapy or antidepressant medication for major depressive disorder. AJP. 2017; 174:533–45.
8. Moda-Sava RN, Murdock MH, Parekh PK, Fetcho RN, Huang BS, Huynh TN, et al. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. Science 2019;364: eaat8078.
9. Ng J, Rosenblat JD, Lui LMW, Teopiz KM, Lee Y, Lipsitz O, et al. Efficacy of ketamine and esketamine on functional outcomes in treatment-resistant depression: A systematic review. J Affect Disord. 2021; 293:285–94.
10. Liu W, Zhou Y, Zheng W, Wang C, Zhan Y, Lan X, et al. Repeated intravenous infusions of Ketamine: neurocognition in patients with anxious and nonanxious treatment-resistant depression. J Affect Disord. 2019;259:1-6.
11. Morris LS, Costi S, Tan A, Stern ER, Charney DS, Murrough JW. Ketamine normalizes subgenual cingulate cortex hyper-activity in depression. Neuropsychopharmacol. 2020;45:1-7.
12. Paul R, Schaaff N, Padberg F, Möller HJ, Frodl T. Comparison of racemic ketamine and S-ketamine in treatment-resistant major depression: report of two cases. World J Biol Psychiatry. 2009;10(3):241-4.
13. M. T. Ketamine in severe, highly treatment-resistant depression—a retrospective case study and a perspective. RG. 2024.
14. Nugroho WS, Konginan A, Sari GM, E. Y. Ketamine Usage Effectivity on Treatment-Resistant Depression Diagnosed Patients: a Scoping Review. JPS. 2024;13(1):63-73.
15. Short B, Fong J, Galvez V, Shelker W, Loo CK. Sideeffects associated with ketamine use in depression: a systematic review. Lancet Psychiatry. 2018;5:65-78.
16. McIntyre RS, Carvalho IP, Lui LMW, Majeed A, Masand PS, Gill H, et al. The effect of intravenous, intranasal, and oral ketamine in mood disorders: a meta-analysis. J Affect Disord 2020; 276:576–84.
17. Chaudhri SI, Amin A, Panjiyar BK, Al-Taie DS, AlEdani EM, Gurramkonda J, et al. A Comparison of the Efficacy and Adverse Effects of Ketamine and Electroconvulsive Therapy in the Management of Treatment-Resistant Depression: A Systematic Review. cureus. 2024;16(3).
18. Pardossi S, Fagiolini A, Scheggi S, A. C. A Systematic Review on Ketamine and Esketamine for Treatment-Resistant Depression and Suicidality in Adolescents: A New Hope? Children (Basel). children. 2024;11(7):801.
19. Brody BD, Park N, Christian A, Shaffer CW, Smetana R, Kotbi N, et al. Ketamine for major depressive disorder during an inpatient psychiatric admission: Effectiveness, adverse events, and lessons learned. J Affect Disord. 2024; 351:293-8.
20. Peters EM, Halpape K, Cheveldae I, Wanson A. Intranasal racemic ketamine for patients hospitalized with treatment-resistant depression: A retrospective analysis. Exp Clin Psychopharmacol. 2023;31(3):593-8.
21. Di Vincenzo JD, Lipsitz O, Rodrigues NB, Lee Y, Gill H, Kratiuk K, et al. Ketamine monotherapy versus adjunctive ketamine in adults with treatment-resistant depression: Results from the Canadian Rapid Treatment Centre of Excellence. Journal of Psychiatric Research. 2021; 143:209-14.
22. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined with a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). Int J neuropsychopharmacol. 2019;22(10):616–30.
23. Siegel JS, Palanca BJA, Ances BM, Kharasch ED, Schweiger JA, Yingling MD, et al. Prolonged ketamine infusion modulates limbic connectivity and induces sustained remission of treatment-resistant depression. Psychopharmacol. 2021;238(4):1157–69.
24. Phillips JL, Norris S, Talbot J, Hatchard T, Ortiz A, Birmingham M, et al. Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. Neuropsychopharmacology. 2020;45(4):606-12.
25. Takahashi N, Yamada A, Shiraishi A, Shimizu H, Goto R, Tominaga Y. Efficacy and safety of fixed doses of intranasal Esketamine as an add-on therapy to Oral antidepressants in Japanese patients with treatment-resistant depression: a phase 2b randomized clinical study. BMC Psychiatry. 2021;21(1):526.
26. Phillips JL, Norris S, Talbot J, Birmingham M, Hatchard T, Ortiz A, et al. Single and repeated ketamine infusions for reduction of suicidal ideation in treatment resistant depression. Neuropsychopharmacol. 2020;45(4):606–12.
27. Hartej G, Barjot G, Nelson B, Orly Lipsitz R, Rosenblat JD, El-Halabi S, et al. The Effects of Ketamine on Cognition in Treatment-Resistant Depression: A Systematic Review and Priority Avenues for Future Research. Neurosci Biobehav Rev. 2021; 120:78-85.