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The use of esketamine in the treatment of patients with severe depression and suicidal ideation: systematic review and meta-analysis

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct, and to assist in the reasoning and decision-making of doctors. The information provided by this project must be critically evaluated by the physician responsible for the conduct that will be adopted, depending on the clinical condition of each patient.
Guideline conclusion: March 2023. Societies: Brazilian Medical Association.

INTRODUCTION

Depression is a very common and disabling mental illness and can be assessed by applying several questionnaires, the most common being the Montgomery-Asberg rating scale[1], scoring on a scale of 0–60, where 7–19 denotes mild depression, 20–34 moderate depression, and greater than 34 severe depression. Major or severe depression is commonly associated with suicidal ideation, resulting in a suicide attempt or suicide.

Esketamine, the S-enantiomer of racemic ketamine, is an antidepressant with a novel mechanism of action. It is a nonselective, noncompetitive antagonist of the N-methyl-D-aspartate receptor and the ionotropic glutamate receptor. It promotes increased stimulation of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) and neurotrophic signaling, which restore brain synaptic function. However, the mechanism by which esketamine exerts its antidepressant effect is unknown. Unlike other antidepressant treatments, the primary antidepressant action of esketamine does not directly involve monoamine, GABA, or opioid receptors[2].

The aim of this systematic review was to evaluate the use of esketamine compared to placebo in patients with severe depression and suicidal ideation.

CLINICAL DOUBT

What is the efficacy and safety of using esketamine in the treatment of patients with severe depression and suicidal ideation?

METHODOLOGY

Eligibility criteria were as follows:

1. Patients with major depression and suicidal ideation.
2. Esketamine treatment plus standard care (antidepressants) compared to placebo plus standard care.
3. Outcomes – improvement in the state of depression, evaluated in appropriate scores.
4. Included randomized controlled trials (RCTs) and observational studies.
5. No restrictions on publication date and language.
6. Full text available for access.
7. Follow-up time: minimum 25 days.

The search for evidence will be carried out in the Medline/PubMed and Central Cochrane virtual scientific information base, using the following search strategy: (Depressive Disorder OR Depressive Disorder, Major OR Depressive Disorder, Treatment-Resistant) AND Esketamine AND Random*. The search in these databases was carried out until the month of

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September 2022. A systematic review was carried out according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[3].

The risk of bias for randomized clinical trials will be assessed using the items of the RoB 2 tool[4], plus other fundamental elements and expressed as low risk, and in some concerns, as high risk of bias. The risk of bias assessment will be carried out by two independent reviewers (AS and IF), and in case of disagreement, a third reviewer (WB) may deliberate on the assessment. The certainty of the evidence will be extrapolated from the risk of bias obtained from the study(ies) (if no meta-analysis) using the GRADE terminology[5] in very low, low, moderate, and high, and through the GRADEpro software[6] (if meta-analysis) into very low, low, moderate, and high.

The measures used to express benefit or harm varied according to the outcomes and were expressed through continuous variables (mean and standard deviation) or categorical variables (absolute number of events). For continuous measurements, the result will be the difference in means (DM) and its standard deviation (SD); for categorical measures, it will be the risk difference (RD) and number needed to treat (NNT) or harm (NNH). The confidence level used is 95%.

When there are common outcomes between the included studies, the results will be expressed through meta-analysis, using the RevMan 5.4 software[7], with the global RD with 95% confidence intervals (CI) being the final measure used to support the synthesis of the evidence, which will answer the clinical question. Estimation of the size of the combined effects was performed by a fixed or random effect model after evaluating the heterogeneity results. Heterogeneity was calculated using the I^2 value.

RESULTS

In the search for evidence, 90 new studies were retrieved; 23 were selected based on title and abstract, of which 3[8-10] were selected to support this evaluation, whose characteristics are described in Table 1 (ANNEXES). The list of those excluded and the reasons are available in the references and Figure 1.

The population included was 524 patients, aged between 18 and 64 years, diagnosed with major depression and suicidal ideation, without associated psychopathy and evaluated using the Montgomery-Asberg Depression Rating Scale with a score ≥22, and confirmed by the Mini International Neuropsychiatric Interview (MINI) (Table 1, ANNEXES).

The exclusion criteria were as follows: bipolar psychiatric disorder, drug addiction, intellectual disability, antisocial personality disorder, borderline personality, and psychotic disorder.

A total of 261 patients received esketamine (84 mg, nasal route, 3 puffs in total, alternating nostrils, with an interval of 5 min, twice a week) associated with treatment with antidepressants, individualized for each patient (*standard-of-care*), and 263 received placebo plus *standard-of-care*.

The primary outcome considered was the reduction of depressive symptoms assessed by the Montgomery-Asberg Depression Rating Scale (MADRS), and the secondary ones were remission of depression (MADRS ≤12), response ≤50% in the reduction of the MADRS score, and serious adverse events.

Regarding the risk of bias, there was no analysis by intention to treat, >20% losses occurred in 3 studies[8-10], and the overall risk of bias can be considered a moderate-to-severe risk. The evaluation was done through the RoB 2 tool (Figure 2).

1. Results of the comparison between the use of esketamine and placebo in participants with major depression and suicidal ideation.
   - 1.1. Mean reduction in MADRS including three studies[8-10] with a total of 522 participants.
     - 1.1.1. One day after the first dose, esketamine may reduce depression rating scale scores over placebo, standardized mean difference (SMD) -3.18, 95%CI -1.58 to -4.78; I^2=0%; p=0.0001 (Figure 3). High evidence certainty (Table 2, ANNEXES).
     - 1.1.2. At the 25-day follow-up, in pre-dose analysis, there was a mean reduction of 2.94 points, SMD -2.94, 95%CI -0.89 to -4.99; I^2=0%; p=0.005, in the esketamine group compared to placebo group (Figure 4). Certainty of moderate evidence.
     - 1.1.3. In a pre-dose analysis and 90-day follow-up, there was a mean reduction of 1.75 points in the esketamine group compared to placebo, SMD -1.75, 95%CI -1.28 to -2.22; I2=89%; p=0.00001 (Figure 5). Very low certainty of evidence.
   - 1.1. Remission rate (≤12 points on the MADRS).
     - 1.1.1. Three studies[8-10], with a total of 522 patients and 24-h follow-up after the first dose, showed a 5% increase in the remission rate with the use of esketamine compared to placebo, RD=-5%, 95%CI -0.1 to -9; I^2=0%; p=0.05, being necessary to treat 20 patients for a benefit (NNT=20) (Figure 6). High evidence certainty.
     - 1.1.2. In a pre-dose analysis, with a follow-up of up to 8 days, two studies[9-10] with a total

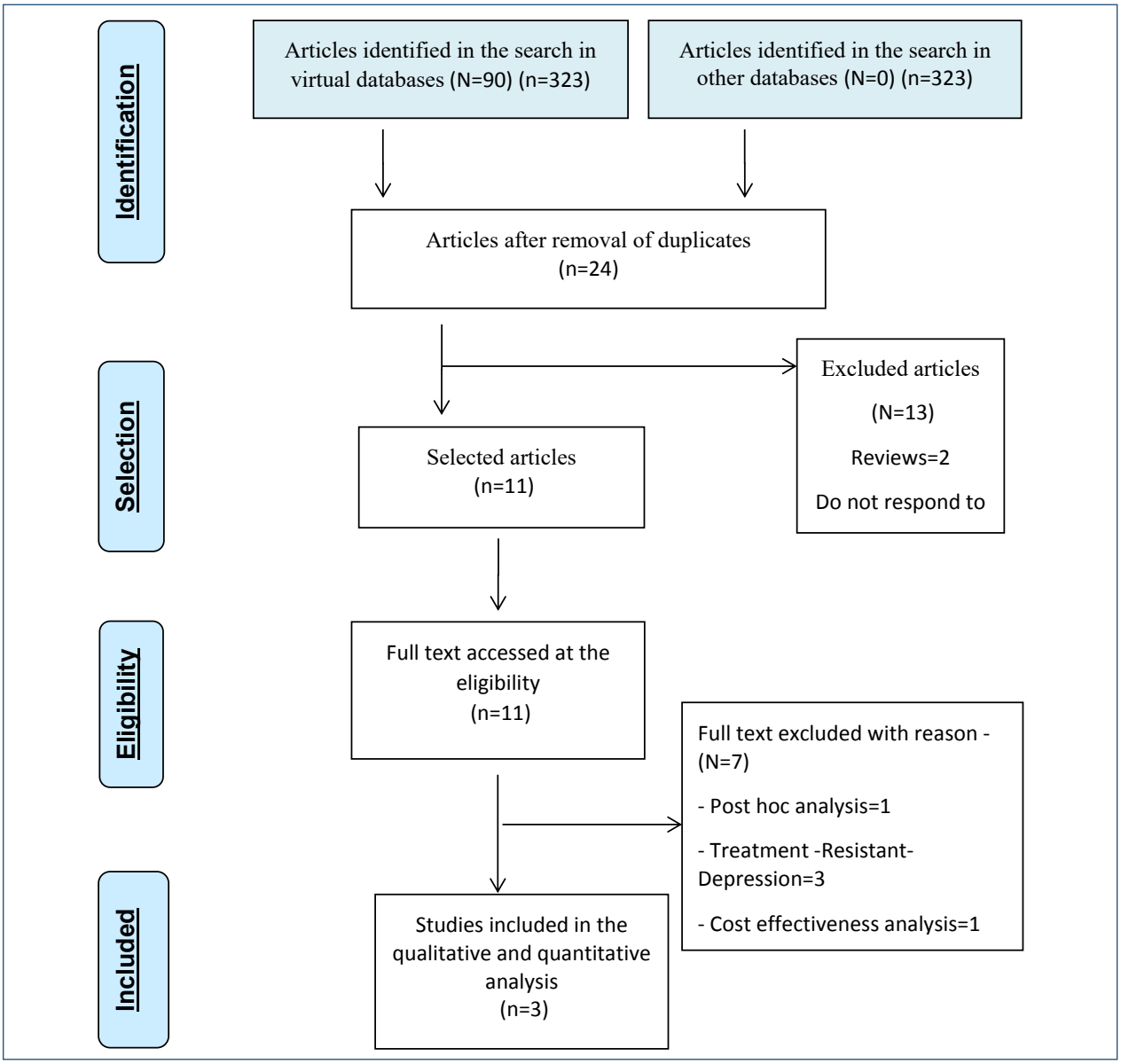

Figure 1. Evidence retrieval and selection diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. https://doi.org/10.1371/journal.pmed1000097

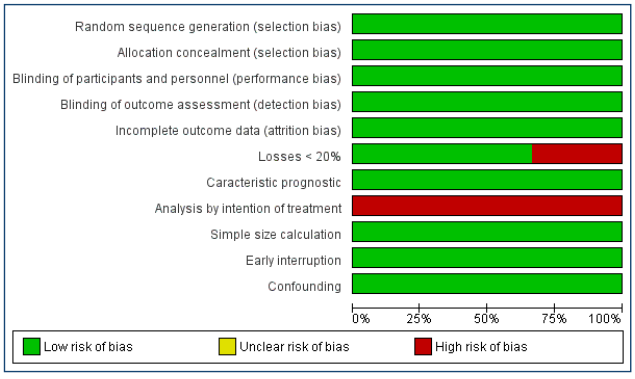

Figure 2. Risk of bias.

of 456 participants showed no difference in the remission rate between groups, RD=5%, 95%CI -3 to 13; p=0.2; I^2=0%; NNT=not significant (NS) (Figure 7). High evidence certainty.

1.1.3. Evaluating the pre-dose 25-day follow-up, three studies[8-10] (522 participants) showed a 12% increase in the remission rate with the use of esketamine compared to placebo, RD=12%, 95%CI 4 to 20; I^2=0%; p=0.004; being necessary to treat 8

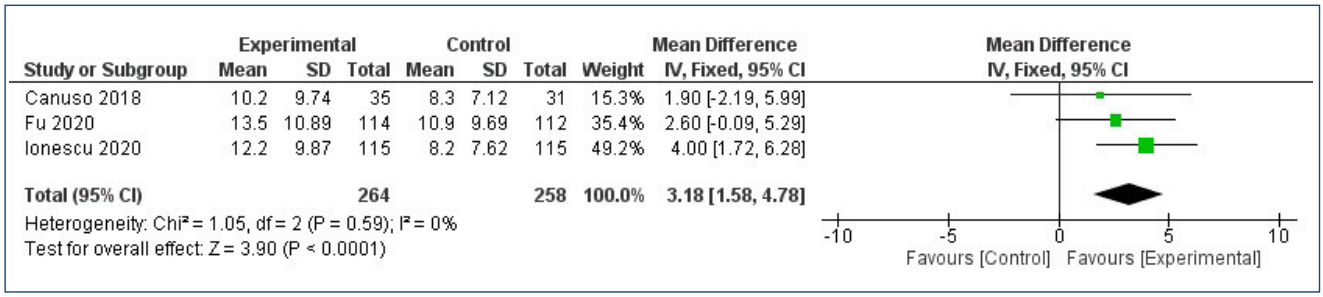

Figure 3. Meta-analysis of the mean reduction in Montgomery-Asberg Rating Scale 1 day after the first dose.

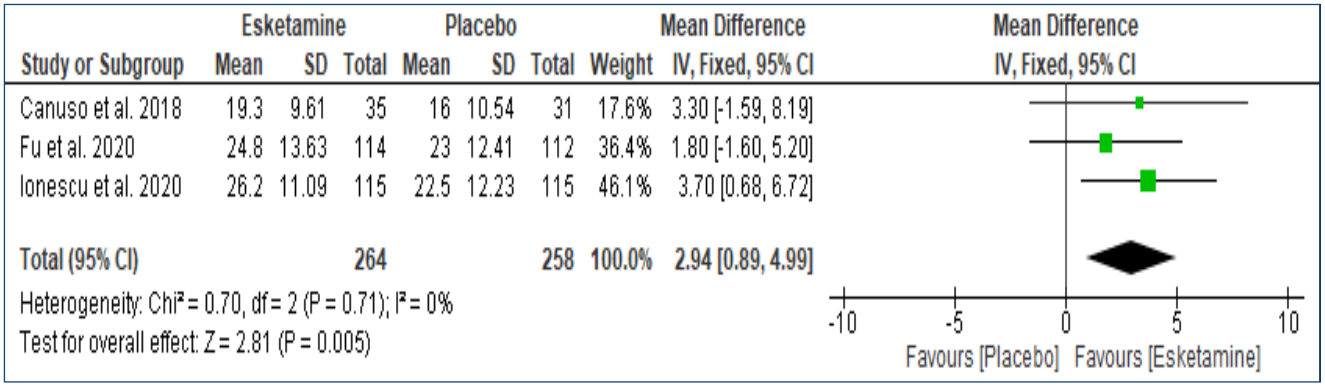

Figure 4. Meta-analysis of mean reduction in Montgomery-Asberg Rating Scale, 25-day follow-up and pre-dose analysis.

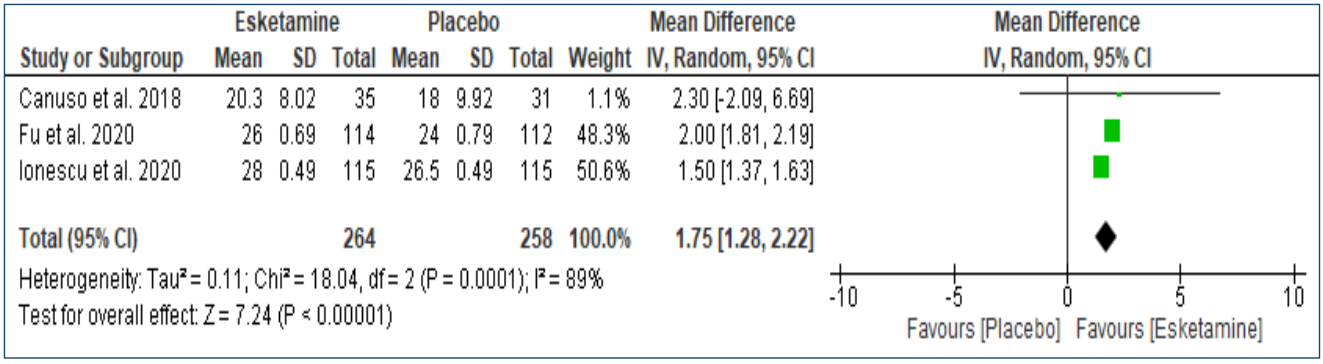

Figure 5. Meta-analysis of mean reduction in Montgomery-Asberg Rating Scale, 90-day follow-up and pre-dose analysis.

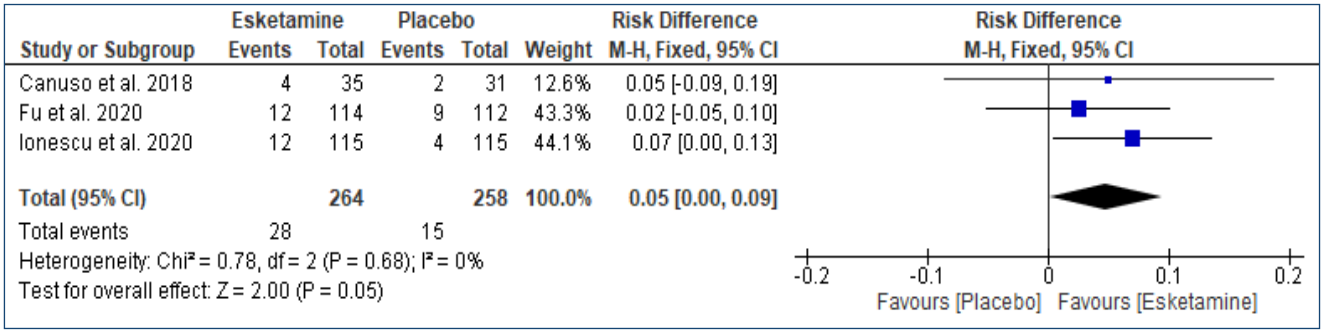

Figure 6. Meta-analysis of the remission rate (reduction ≤12 points on the Montgomery-Asberg Rating Scale), 24 h after the first dose.

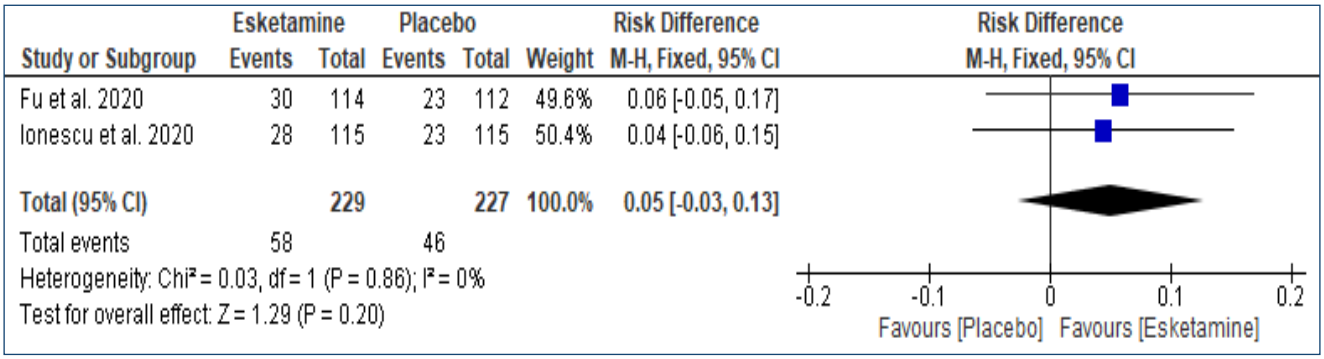

Figure 7. Meta-analysis of the 8-day remission rate and pre-dose analysis.

patients for a benefit (NNT=8) (Figure 8). Certainty of moderate evidence.

1.2. Response rate with ≥50% reduction in initial MADRS points, esketamine versus placebo.

1.2.1. Two studies[8-10] (296 participants), 24 h post-dose follow-up, showed an increase of 18% in the response rate, in patients who used esketamine compared to placebo, RD=18%, 95%CI 9 to 26; I^2=0%, p=0.00001; NNT=6 (Figure 9). High evidence certainty.

1.2.2. There was no difference between the groups when we evaluated in the follow-up for 8 days, in one study[10] (230 participants), RD=3%, 95%CI -9 to 16; p=0.59; NNT=NS (Figure 10). High evidence certainty.

1.2.3. In 25-day follow-up and pre-dose analysis, two studies[8-10] (296 participants) showed no difference between groups, RD=7, 95%CI -12 to 26, I^2=57%, p=0.13, NNT=NS (Figure 11). Certainty of moderate evidence.

1.3. Serious adverse events.

1.3.1. Three studies[8-10], with a total of 522 patients in a 25-day follow-up and pre-dose analysis, showed no difference when comparing esketamine versus placebo, RD=2%, 95%CI -2 to 5, I^2=43%, p=0.30, NNH=NS (Figure 12). Very low certainty of evidence.

EVIDENCE SUMMARY

The use of esketamine in patients with major depression and suicidal ideation was compared to placebo.

- It reduces depression rating scale scores (MADRS), standardized mean difference of 3.18 points, and 24 h after the first dose. High evidence certainty.
- It reduces depression rating scale scores (MADRS), standardized mean difference of 2.94 points, and pre-dose analysis in the 25-day follow-up. Certainty of moderate evidence.
- It reduces depression rating scale scores (MADRS), standardized mean difference of 1.75 points, and pre-dose analysis in the 90-day follow-up. Low certainty of evidence.
- It increases the remission rate by 5% (MADRS ≤12 points), NNT=20, in 24 h after the first dose of treatment. High evidence certainty.
- There is no difference in remission rate at 8-day follow-up and pre-dose analysis. High evidence certainty.
- Increases remission rate by 12% (MADRS ≤12 points), NNT=8, at 25 days and pre-dose analysis. Certainty of moderate evidence.
- 18% increase in response rate (≥50% point reduction from baseline MADRS), NNT=6, within 24 h after first dose. High evidence certainty.
- There is no difference in response rate at 8-day follow-up and pre-dose analysis. High evidence certainty.
- There is no difference in response rate at 25-day follow-up and pre-dose analysis. High evidence certainty.
- There is no difference in the number of serious adverse events within 25 days. Very low certainty of evidence.

DISCUSSION

Countless deaths in the world are due to suicide, and people with severe depression are vulnerable to suicidal ideation. According to the World Health Organization (WHO)[11], approximately

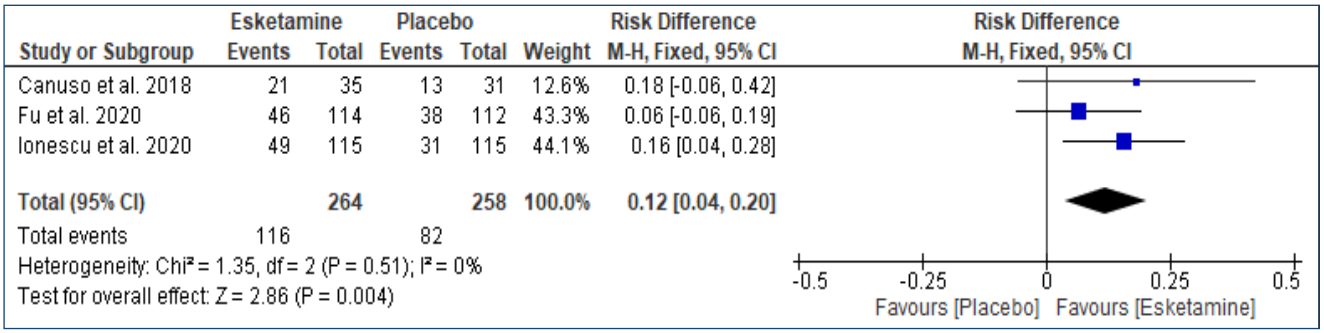

Figure 8. Meta-analysis of depression remission results with esketamine, 25 days and pre-dose analysis.

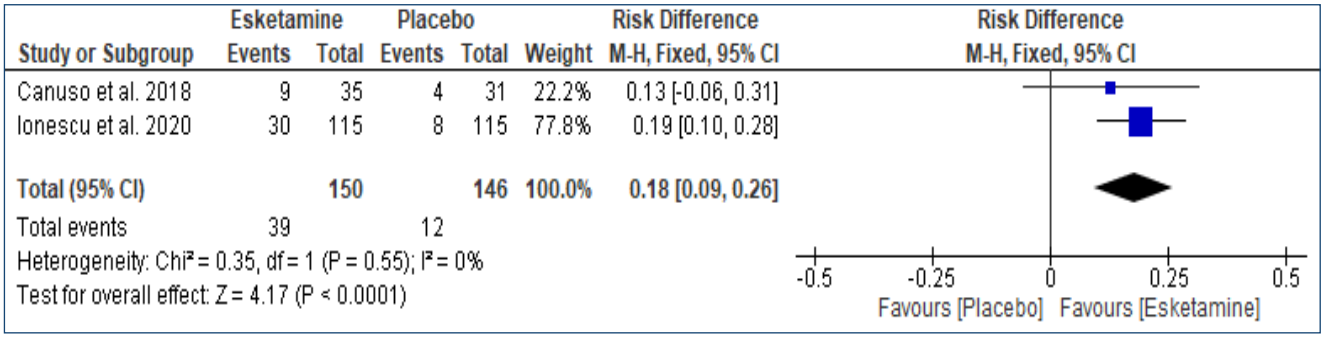

Figure 9. Meta-analysis of response rate at 24 h post-dose follow-up.

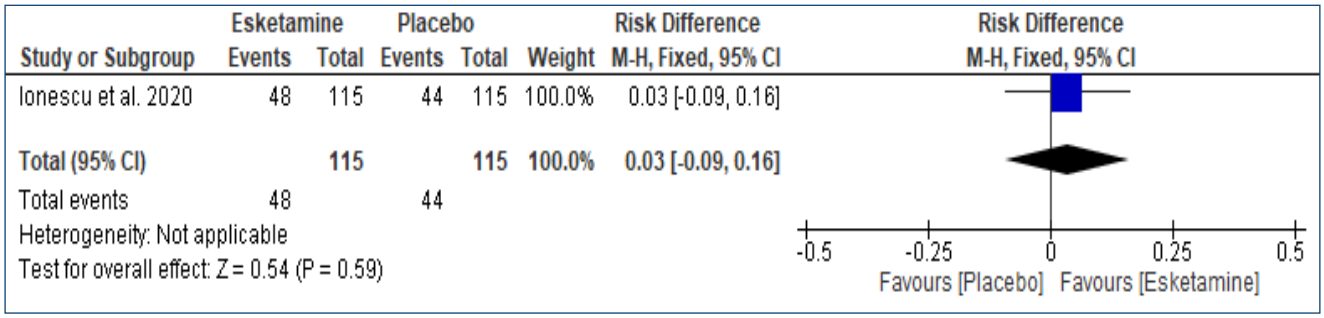

Figure 10. Meta-analysis of response rate reduction, 8-day pre-dose follow-up.

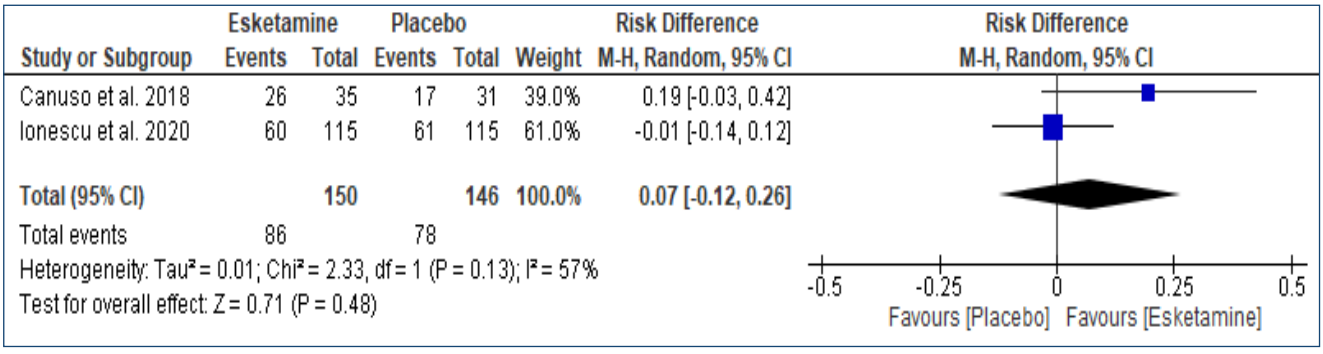

Figure 11. Meta-analysis of response rate reduction, 25-day follow-up and pre-dose analysis.

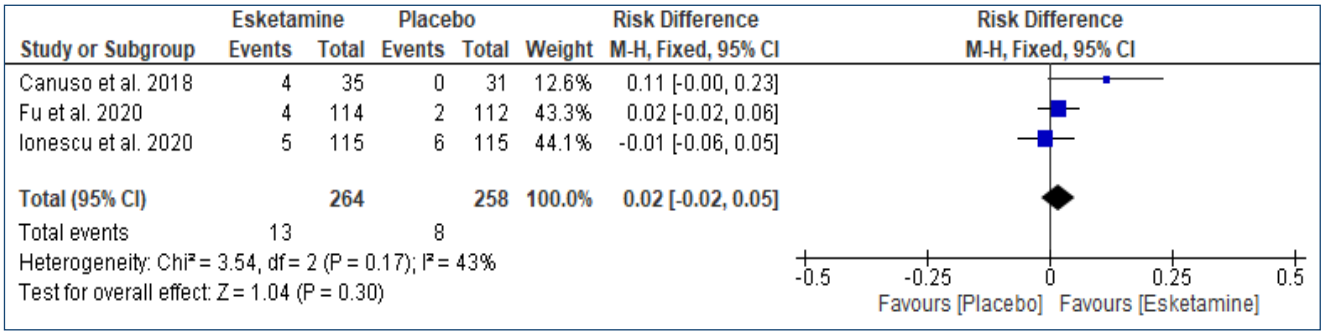

Figure 12. Meta-analysis of adverse events, 25-day follow-up and pre-dose analysis.

700,000 people commit suicide worldwide, influenced by numerous psychological, social, and cultural factors.

In this systematic review with meta-analysis, we aggregated only studies that used esketamine in patients with depression and suicidal ideation in the search for evidence of efficacy and safety.

In the primary outcome, which measured the reduction in the score on the Montgomery-Asberg Depression Rate Score, used to grade levels of depression, we obtained a standardized mean reduction of 3.18 points with the use of esketamine and individualized antidepressants in comparison with placebo and individualized antidepressants. It should be noted that all patients included had a MADRS score of ≥22.

For another evaluated endpoint, which was the remission rate (MADRS ≤12 points), esketamine, compared to placebo, showed a benefit with a reduction of 5% (NNT=20) in 1 day after the first dose and 12% (NNT=8) at the 25-day follow-up and pre-dose analysis.

Regarding death by suicide: there was no death in both groups (esketamine/placebo) in a follow-up of up to 90 days.

Esketamine has been shown to be a fast-acting treatment for patients with severe depression and suicidal ideation; however, responses to treatment are often transient, and the antidepressant action of esketamine lacks robust clinical durability; studies with long follow-up are lacking. Little is known about which patient characteristics are associated with more rapid esketamine responses and/or more durability.

Esketamine is shown to be safe without increasing serious adverse events.

CONCLUSION

The use of esketamine and *standard-of-care* compared to placebo in patients with major depression (MADRS >22 points) and suicidal ideation reduces scores by an average of 3.18 and 2.94 points, respectively, in the follow-ups of 24 h post-dose and 25 days pre-dose.

There is an increase in response rate (≥50% reduction in baseline MADRS points) by 18% at 24 h follow-up after the first dose, and there is no difference at 25-day follow-up and pre-dose analysis.

Therefore, it is concluded that patients with major depression and suicidal ideation benefit from the use of esketamine 84 mg, nasal spray 1 puff 3 times, with an interval of 5 min, twice a week for 4 weeks, associated with antidepressants, in follow-up for up to 25 days.

AUTHORS' CONTRIBUTIONS

IF: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **AS:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **WMB:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Montgomery SA, Asberg M. A new depression scaledesigned to be sensitive to change. Br J Psychiatry. 1979;134(4):382-9. https://doi.org/10.1192/bjp.134.4.382

2. Wei Y, Chang L, Hashimoto K. Molecular mechanisms underlying the antidepressant actions of arketamine: beyond the NMDA receptor. Mol Psychiatry. 2022;27(1):559-73. https://doi.org/10.1038/s41380-021-01121-1

3. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
4. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
5. GRADE Working Group. [cited on Sep 2021]. Available from: https://www.gradeworkinggroup.org/
6. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University; 2020 (developed by Evidence Prime, Inc.). Available from: gradepro.org
7. Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.
8. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, et al. 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. Am J Psychiatry. 2018;175(7):620-30. https://doi.org/10.1176/appi.ajp.2018.17060720
9. Fu DJ, Ionescu DF, Li X, Lane R, Lim P, Sanacora G, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: double-blind, randomized study (ASPIRE I). J Clin Psychiatry. 2020;81(3):19m13191. https://doi.org/10.4088/JCP.19m13191
10. Ionescu DF, Fu DJ, Qiu X, Lane R, Lim P, Kasper S, et al. Esketamine nasal spray for rapid reduction of depressive symptoms in patients with major depressive disorder who have active suicide ideation with intent: results of a phase 3, double-blind, randomized study (ASPIRE II). Int J Neuropsychopharmacol. 2021;24(1):22-31. https://doi.org/10.1093/ijnp/pyaa068
11. Suicide (Dashboard), World Health Organization. [cited on 2022 Nov 5]. Available from: https://www.who.int/news-room/fact-sheets/detail/suicide

ANNEXES

Table 1. Characteristics of clinical studies evaluating the use of esketamine compared to placebo.

Studies	Population	Intervention	Comparison	Outcome	Follow-up
Canuso CM 2018	The study selected 68 participants (19–64 years old) who had a diagnosis of severe depressive disorder (DMD) with active suicidal ideation, without psychotic characteristics according to DSM-IV-TR criteria and confirmed by applying the Mini International Neuropsychiatric Interview (MINI). Participants scored ≥22 on the Montgomery-Åsberg Depression Rating Scale (MADRS). Several psychiatric comorbidities were excluded: current diagnosis of bipolar disorder, moderate-to-severe substance use disorder, intellectual disability, antisocial personality disorder, current diagnosis of borderline personality disorder, or past psychotic disorder.	Esketamine 84 mg, nasal spray 1 puff, 3 times, 5 min apart, twice a week, for 4 weeks, associated with antidepressants.	Placebo and antidepressants.	Primary: mean reduction in MADRS scale score. Secondary: remission of depression (MADRS ≤12), response ≤50% in MADRS score reduction, and adverse events.	80 days with segmentation in the first 25 days.
Fu DJ, 2020 (ASPIRE I)	Phase 3, multicenter, double-blind study (ASPIRE I), conducted between June 2017 and December 2018, 226 adult participants (18–64 years old) with a diagnosis of major depressive illness (DMD) and suicidal ideation, without psychotic features according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), confirmed by MINI. Eligibility criteria required patients to respond affirmatively to mini-questions B3 ("Have thoughts of suicide [killing yourself]?") and B10 ("Do you intend to take action or have thoughts of killing yourself in the past 24 hours?") within 24 h of randomization, be in clinical need of acute psychiatric hospitalization due to imminent risk of suicide, and >28 pre-dose MADRS points on day 1.	Esketamine 84 mg, nasal spray 1 puff, 3 times, 5 min apart, twice a week, for 4 weeks, associated with antidepressants.	Placebo and antidepressants.	Primary: mean reduction in MADRS scale score. Secondary: remission of depression (MADRS ≤12), response ≤50% in MADRS score reduction and adverse events, and change in CGI-SS-r score 24 h after the first dose.	90 days with segmentation in the first 25 days.
Ionescu DF 2021 (ASPIRE II)	Study conducted with 230 randomized patients (115 per arm), multicenter, double-blind (ASPIRE II) between June 2017 and April 2019. Eligible patients were between 18 and 64 years old, complied with the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5) criteria for MDD (without psychosis) based on diagnostic assessment using MINI questionnaire and MADRS score >28.	Esketamine 84 mg, nasal spray 1 puff, 3 times, 5 min apart, twice a week, for 4 weeks, associated with antidepressants.	Placebo and antidepressants.	Primary: mean reduction in MADRS scale score. Secondary: remission of depression (MADRS ≤12), response ≤50% in MADRS score reduction and adverse events, and change in CGI-SS-r score 24 h after the first dose.	90 days with segmentation in the first 25 days.

MDD: major depressive disorder.

Table 2. Quality of evidence (GRADE).

Certainty assessment							No. of patients		Effect		Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Esketamine	Placebo	Relative (95%CI)	Absolute (95%CI)	
Average MADRS reduction, up to 24 h after the first dose (follow-up: mean 1 days)											
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	264	258	-	MD 3.18 points at MADRS higher (1.58 higher to 4.77 higher)	⊕⊕⊕⊕ High
MADRS average reduction in 25 days, pre-dose											
3	Randomized trials	Serious [a]	Not serious	Not serious	Not serious	None	264	258	-	MD 2.94 points at MADRS higher (0.9 higher to 4.98 higher)	⊕⊕⊕◯ Moderate
MADRS average reduction, pre-dose, up to 90 days											
3	Randomized trials	Serious [a]	Very serious[b]	Not serious	Not serious	None	264	258	-	DM 1.75 points at MADRS higher (1.28 higher to 2.22 higher)	⊕◯◯◯ Very low
Response ≥50% in reduction in baseline MADRS. Follow-up 1 day post-dose											
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	39/150 (26.0%)	12/146 (8.2%)	RR 3.14 (1.72–5.74)	**180 fewer per 1,000** (from 260 fewer to 90 fewer)	⊕⊕⊕⊕ High
Response ≥50% in reduction in baseline MADRS. Follow-up 8 days, pre-dose											
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	48/115 (41.7%)	44/115 (38.3%)	RR 1.09 (0.79–1.50)	**30 fewer per 1,000** (from 160 fewer to 90 more)	⊕⊕⊕⊕ High
Response ≥50% in reduction in baseline MADRS. Follow-up 25 days pre-dose											
2	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	86/150 (57.3%)	78/146 (53.4%)	RR 1.07 (0.87–1.31)	**40 fewer per 1,000** (from 150 fewer to 80 more)	⊕⊕⊕◯ Moderate
Remission of depression, ≤12 points on the MADRS. Follow-up 1 day post-dose											
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	28/264 (10.6%)	15/258 (5.8%)	RR 1.82 (1.00–9.03)	**50 fewer per 1,000** (from 90 fewer to 0 fewer)	⊕⊕⊕⊕ High
Remission of depression, ≤12 points on the MADRS. Follow-up 8 days pre-dose											
2	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[c]	None	58/229 (25.3%)	46/227 (20.3%)	RR 1.25 (0.89–1.76)	**50 fewer per 1,000** (from 130 fewer to 30 more)	⊕◯◯◯ Very low
Remission of depression, ≤12 points on the MADRS. 25-day pre-dose follow-up											
3	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	116/264 (43.9%)	82/258 (31.8%)	RR 1.38 (1.10–1.72)	**120 fewer per 1,000** (from 200 fewer to 40 fewer)	⊕⊕⊕◯ Moderate
Serious adverse events within 25 days											
3	Randomized trials	Serious[a]	Not serious	Not serious	Extremely serious[c]	None	13/261 (5.0%)	8/263 (3.0%)	RR 1.62 (0.70–3.73)	**20 fewer per 1,000** (from 50 fewer to 10 more)	⊕◯◯◯ Very low

CI: confidence interval; MD: mean difference; RR: risk ratio. [a]There was no analysis by intention of treatment and losses >20%. [b]Heterogeneity 89%. [c]Confidence interval exceeds the nullity line. There was no analysis by intention to treat and losses >20%. Heterogeneity 89%. Confidence interval crosses the null line.
Patient or population: Patients with major depression and suicidal ideation
Context: Efficacy, safety, and tolerability
Intervention: Esketamine
Comparison: Placebo

EXCLUDED STUDIES (REASONS)

Agboola F, Atlas SJ, Touchette DR, Fazioli K, Pearson SD. The effectiveness and value of esketamine for the management of treatment-resistant depression. J Manag Care Spec Pharm. 2020;26(1):16-20. https://doi.org/10.18553/jmcp.2020.26.1.16. (Cost-effectiveness analysis).

Bahji A, Vazquez GH, Zarate CA. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord. 2021;278:542-55. https://doi.org/10.1016/j.jad.2020.09.071. (Systematic review).

Smith-Apeldoorn SY, Veraart JKE, Kamphuis J, Asselt ADI, Touw DJ, Aan Het Rot M, et al. Oral esketamine for treatment-resistant depression: rationale and design of a randomized controlled trial. BMC Psychiatry. 2019;19(1):375. https://doi.org/10.1186/s12888-019-2359-1. (Protocol).

Correia-Melo FS, Leal GC, Vieira F, Jesus-Nunes AP, Mello RP, Magnavita G, et al. Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: a randomized, double-blind, non-inferiority study. J Affect Disord. 2020;264:527-34. https://doi.org/10.1016/j.jad.2019.11.086. (Does not meet eligibility criteria).

Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2019;76(9):893-903. https://doi.org/10.1001/jamapsychiatry.2019.1189. (does not meet eligibility criteria).

Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2018;75(2):139-48. https://doi.org/10.1001/jamapsychiatry.2017.3739. (does not meet eligibility criteria).

Diekamp B, Borentain S, Fu DJ, Murray R, Heerlein K, Zhang Q, et al. Effect of concomitant benzodiazepine use on efficacy and safety of esketamine nasal spray in patients with major depressive disorder and acute suicidal ideation or behavior: pooled randomized, controlled trials. Neuropsychiatr Dis Treat. 2021;17:2347-57. https://doi.org/10.2147/NDT.S314874. (Post hoc Analysis).

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. https://doi.org/10.1093/ijnp/pyz039. (Does not meet eligibility criteria).

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. https://doi.org/10.1016/j.jad.2021.06.032. (Systematic review).

Jones RR, Freeman MP, Kornstein SG, Cooper K, Daly EJ, Canuso CM, et al. Efficacy and safety of esketamine nasal spray by sex in patients with treatment-resistant depression: findings from short-term randomized, controlled trials. Arch Womens Ment Health. 2022;25(2):313-26. https://doi.org/10.1007/s00737-021-01185-6. (Post hoc Analysis).

Katz EG, Hough D, Doherty T, Lane R, Singh J, Levitan B. Benefit-risk assessment of esketamine nasal spray vs. placebo in treatment-resistant depression. Clin Pharmacol Ther. 2021;109(2):536-46. https://doi.org/10.1002/cpt.2024. (Post hoc Analysis).

Nijs M, Wajs E, Aluisio L, Turkoz I, Daly E, Janik A, et al. Managing esketamine treatment frequency toward successful outcomes: analysis of phase 3 data. Int J Neuropsychopharmacol. 2020;23(7):426-33. https://doi.org/10.1093/ijnp/pyaa027. (Post hoc Analysis).

Papakostas GI, Salloum NC, Hock RS, Jha MK, Murrough JW, Mathew SJ, et al. Efficacy of esketamine augmentation in major depressive disorder: a meta-analysis. J Clin Psychiatry. 2020;81(4):19r12889. https://doi.org/10.4088/JCP.19r12889. (Review Article).

Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. Am J Psychiatry. 2019;176(6):428-38. https://doi.org/10.1176/appi.ajp.2019.19020172. (Does not meet eligibility criteria).

Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, et al. Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression-TRANSFORM-3. Am J Geriatr Psychiatry. 2020;28(2):121-41. https://doi.org/10.1016/j.jagp.2019.10.008. (Does not meet eligibility criteria).

Targum SD, Daly E, Fedgchin M, Cooper K, Singh JB. Comparability of blinded remote and site-based assessments of response to adjunctive esketamine or placebo nasal spray in patients with treatment resistant depression. J Psychiatr Res. 2019;111:68-73. https://doi.org/10.1016/j.jpsychires.2019.01.017. (Pilot study).

Targum SD, Daly E, Fedgchin M, Cooper K, Singh JB. Comparability of blinded remote and site-based assessments of response to adjunctive esketamine or placebo nasal spray in patients with treatment resistant depression. J Psychiatr Res. 2019;111:68-73. https://doi.org/10.1016/j.jpsychires.2019.01.017. (Does not meet eligibility criteria).

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. https://doi.org/10.1186/s12888-021-03538-y. (Does not meet eligibility criteria).

Turkoz I, Daly E, Singh J, Lin X, Tymofyeyev Y, Williamson D, et al. Treatment response with esketamine nasal spray plus an oral antidepressant in patients with treatment-resistant depression without evidence of early response: a pooled post hoc analysis of the TRANSFORM studies. J Clin Psychiatry. 2021;82(4):20m13800. https://doi.org/10.4088/JCP.20m13800. (Post hoc Analysis).

Vázquez GH, Bahji A, Undurraga J, Tondo L, Baldessarini RJ. Efficacy and tolerability of combination treatments for major depression: antidepressants plus second-generation antipsychotics vs. esketamine vs. lithium. J Psychopharmacol. 2021;35(8):890-900. https://doi.org/10.1177/02698811211013579. (Does not meet eligibility criteria).

Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). J Clin Psychiatry. 2020;81(3):19m12891. https://doi.org/10.4088/JCP.19m12891. (Does not meet eligibility criteria).