GUIDELINE

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# The use of esketamine in the treatment of patients with oral antidepressant-resistant depression: 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 conditions and the clinical condition of each patient.
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## INTRODUCTION

Depression is a very common disabling mental illness and can be assessed through the application of several questionnaires, one of the most commonly used being the Montgomery-Asberg rating scale[1], scoring from 0 to 60, where 7–9 ranks mild depression, 20–24 ranks moderate depression, and greater than 34 ranks severe depression. Approximately one-third of patients with major depression do not experience remission when treated with up to two or more oral antidepressants (OAD), being considered treatment-resistant[2].

In *post-mortem* analysis, in vivo gene expression studies and brain imaging data suggest abnormalities in glutaminergic signaling in the pathophysiology of depression[3,4], allowing the use of new antidepressants with a mechanism of action outside the monoaminergic system.

Esketamine, which is the S-enantiomer of racemic ketamine, is an antidepressive drug with a novel mechanism of action. This active drug is a non-selective, non-competitive *N*-methyl-*D*-aspartate receptor (NMDAR) antagonist; being an ionotropic glutamate receptor, it promotes increased stimulation of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) and neurotrophic signaling that restore brain synaptic function. However, the mechanism by which esketamine exerts its antidepressive effect is unknown. Unlike other antidepressive treatments, the primary antidepressive action of esketamine does not directly involve monoamine, GABA, or opioid receptors[5].

The aim of this systematic review was to evaluate the use of esketamine in comparison with placebo in patients with resistant depression.

### Clinical doubt

What is the efficacy and safety of using esketamine in the treatment of patients with resistant depression?

## METHODOLOGY

Eligibility Criteria:

1. Patients with resistant depression;
2. Compared to placebo plus standard care;
3. Outcomes – improvement in the state of depression, evaluated with appropriate scores;
4. Included randomized controlled trials (RCTs);
5. No restrictions on the date of publication, age of participants, and language;
6. Full text available for access;
7. Follow-up time: minimum of 28 days.

The search for evidence will be carried out in the virtual scientific information database Medline/Pubmed, CENTRAL COCHRANE, and ClinicalTrials.gov, using the search strategy:

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(Depressive Disorder OR Depressive Disorder, Major OR Depressive Disorder, Treatment-Resistant) AND Esketamine AND Random*. The search in these databases was carried out until December 2022. This systematic review will be prepared according to the recommendations contained in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[6], and the protocol of this study has been registered in PROSPERO (CRD42023403453).

The risk of bias for randomized clinical trials will be assessed using the items in version 2 of the Cochrane risk of bias tool for randomized clinical trials RoB 2[7] plus other fundamental elements and expressed as low risk, some concerns, and high risk of bias. The risk of bias assessment will be conducted by two independent reviewers (AS and IF), and in case of disagreements, 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 there is no meta-analysis) using the terminology GRADE[8] in very low, low, moderate, and high and through the GRADEpro software[9] (if meta-analysis) into very low, low, moderate, and high.

The measures used to express benefit or harm varied according to the outcomes, being expressed through continuous variables (mean and standard deviation (SD)) or categorical variables (absolute number of events). For continuous measurements, the result will be the difference in means (DM) and its 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 among the included studies, patients and results will be added together, with different doses (esketamine 28–84 mg/week) for comparison with placebo. For calculation in absolute numbers or averages that can be paired, the results will be meta-analyzed using the RevMan 5.4 software[10], 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 doubts. The estimation of the size of the combined effects will be carried out by a fixed or random effect model after the evaluation of the heterogeneity results. Heterogeneity was calculated using the $I^2$ value.

## RESULTS

In the search for evidence, 90 studies were retrieved, 27 being selected by title and abstract, of which 3[11-13] 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 and Table 2.

The population included was 703 patients, aged over 18 years, diagnosed with recurrent depression or a depressive episode for a period ≥2 years, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria (DMS-5 criteria) and without associated psychotic disorders, confirmed by the Mini International Neuropysichiatric Interview (MINI) (Table 1 – ANNEXES). Participants had episodes of moderate to severe depression, with a score≥28 when assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) or a score≥34 when assessed using the Inventory of Depressive Symptomatology.

Exclusion criteria were bipolar psychiatric disorder, drug addiction, intellectual disability, antisocial personality disorder, *borderline personality*, and psychotic disorder.

A total of 415 participants received esketamine for 4 weeks (28–84 mg, nasal route, 3 *puffs* in total, alternating nostrils, 5 min apart, twice a week) associated to treatment with oral antidepressants, individualized for each patient (*standard of care*), and 288 received placebo plus *standard of care*.

The primary outcome considered was the reduction in depressive symptoms assessed by the MADRS and the secondary ones were remission of depression (MADRS score ≤12) and response ≤50% in the reduction in the MADRS score initial and adverse events.

Regarding the risk of bias (Figure 2), two studies did not present analysis by intention to treat[10,11], and the overall risk of bias can be considered moderate. The evaluation was through the ROB 2 tool.

### Results of comparing esketamine versus placebo in patients with resistant depression at 28-day follow-up

The evaluation of MADRS score reduction included three studies[11-13] with a total of 681 patients. The meta-analysis for this outcome showed a mean reduction of 4.09 points in favor of using esketamine compared to placebo (MD=-4.09, 95%CI -5.73 to -2.45, $I^2$=0%, p=0.00001, Figure 3; moderate evidence certainty, Table 3 – ANNEXES).

The meta-analysis for the outcome rate of patients in "remission" (MADRS≤12 points) included three studies[11-13] with a total of 703 participants. Compared with placebo, esketamine increased the number of patients with "remission" by 10% (RD=0.10, 95%CI 0.03–0.17; $I^2$=8%, p=0.004), requiring treatment (NNT) of 10 patients for one get "remission" (Figure 4; moderate evidence certainty, Table 3 – ANNEXES).

Three studies[11-13], including a total of 703 patients, were included to meta-analyze the outcome "≥50% reduction in baseline MADRS score." Compared to placebo, esketamine increased the number of patients with "≥50% reduction in

baseline score" by 11% (RD=0.11%, 95%CI 0.05–0.16, $I^2$=8%, p=0.0001; NNT=9), (Figure 5; moderate evidence certainty, Table 3 – ANNEXES).

Serious adverse events were evaluated in three studies[11-13], with a total of 703 participants, in a 28-day follow-up and showed no difference when comparing esketamine versus placebo (RD=1%, 95%CI -0.01 to 0.03, $I^2$=8%, p=0.36; NNH=NS) (Figure 6; very low certainty of evidence).

## Evidence summary

The use of esketamine over a period of 4 weeks (28–84 mg, nasal route, 3 *puffs* in total, alternating nostrils, with an interval of 5

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

| Studies | Population | Intervention | Comparison | Outcome | Follow-up |
|---|---|---|---|---|---|
| Fedgchin (TRANSFORM-1) 2019 | The study was randomized, double-blind and multicenter, with 346 participants aged between 18 and 64 years old with recurrent major depression or a single episode of depression for more than 2 years, without psychotic characteristics according to DSM-IV-TR criteria and confirmed by Mini International. ***Neuropsychiatric Interview(MINI)***. Participants scored ≥28 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and scored ≥34 on the ***Inventory of Depressive Symptomatolgy***. Several psychiatric comorbidities were exclusionary: suicidal ideation, current diagnosis of bipolar disorder, moderate to severe substance use disorder, and substance use. | Esketamine 56 and 84 mg, nasal spray twice a week for 4 weeks, combined 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 | 4 weeks |
| Popova (TRANSFORM-2) 2019 | Phase 3, double-blind multicenter study, conducted between June 2017 and December 2018, N=227 adult participants (18–64 years old) diagnosed with major depressive illness (DMD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), without psychotic features confirmed by application of the ***Mini International Neuropsychiatric Interview*** (MINI); having a score ≥34 on the "***Inventory of Depressive Symptomatolgy (IDS-C)***" scale. Exclusion criteria: suicidal ideation, psychotic disorders, and drug use. | Esketamine 56–84 mg nasal spray twice a week for 4 weeks plus 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 | 4 weeks |
| Ochs-Ross (TRANSFORM-3) 2019 | Randomized, phase 3, double-blind, actively controlled, multicenter study conducted in 13 countries between August 2015 and August 2017. 138 participants were selected (N=72 esketamine/antidepressants and N=66 placebos/antidepressants. Eligible patients were aged ≥65 years old, diagnosed with major depressive illness (DMD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), treated with ≥2 oral antidepressants, without psychotic features confirmed by applying the Mini International ***questionnaire Neuropsychiatric Interview*** (MINI) Exclusion criteria were suicidal ideation, psychotic disorders, and drug use. | Esketamine 28–84 mg nasal spray twice a week for 4 weeks plus 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 | 4 weeks |

min, twice a week) associated with treatment with oral antidepressants, in patients with drug-resistant depression treatment with oral antidepressants compared to placebo:

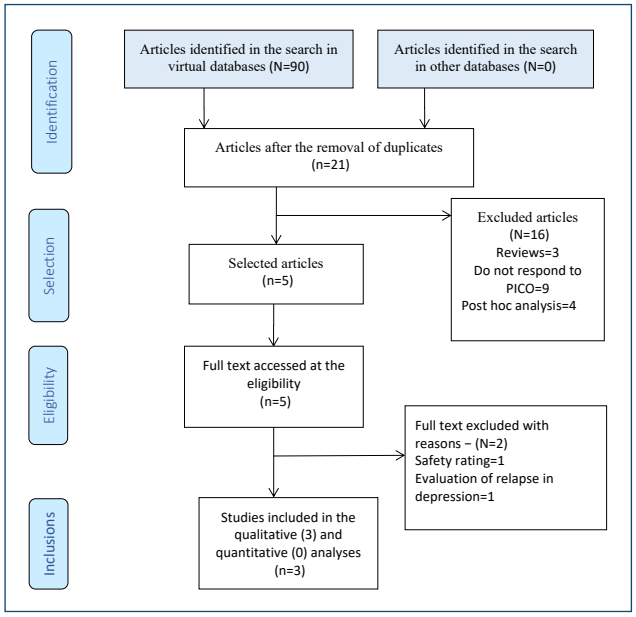


**Figure 1.** Diagram in recovery and selection of evidence. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed1000097

- It reduces depression rating scale scores (MADRS), standardized mean of 4.09 points on the MADRS. Moderate evidence certainty.
- It increases the "remission" rate by 10% (MADRS≤12 points); NNT=10. Certainty of moderate evidence.
- It increases the number of patients with reduction by 11%≥50% points on the MADRS initial; NNT=9. Certainty of moderate evidence.
- There is no difference in the number of serious adverse events. Very low certainty of evidence.

## DISCUSSION

In this systematic review with meta-analysis, only randomized clinical trials were included, which evaluated the use of esketamine in comparison with placebo, in patients with depression resistant to treatment with two or more oral antidepressants (OAD).

The use of esketamine plus individualized antidepressants compared to placebo showed a reduction standardized mean of 4.09 points on the Montgomery-Asberg scale for depression. It should be noted that all patients included had scores≥28 points on the MADRS. In secondary endpoints, the remission rate (MADRS score≤12) and the ≥50% reduction in the baseline MADRS showed a benefit of 10% (NNT=10) and 11% (NNT=9), respectively, at the 28-day follow-up.

**Table 2.** Studies with exclusion reasons.

| Studies | Reason for exclusion |
|---|---|
| Agboola 2020 | Cost-effectiveness analysis |
| Anees Bahji 2020 | Systematic review |
| Nickname 2019 | Protocol |
| Correia-Melo 2020 | Does not meet eligibility criteria |
| Daly 2017 | Purpose of the study was to evaluate the relapse of depression in stable patients who do not meet the PICO |
| Diekamp 2021 | Post hoc analysis of two ASPIRE I and ASPIRE II studies |
| Fedghin 2019 | Depression resistant to conventional antidepressants |
| Jason Ng 2021 | Systematic review |
| Jones 2022 | Post hoc analysis, secondary outcome |
| Katz 2020 | Post hoc analysis of three studies |
| Nijs 2020 | Post hoc analysis |
| Papakostas 2020 | Review article |
| SD Targum 2019 | Pilot study |
| Singh 2016 | Does not meet eligibility criteria |
| Takahashi 2021 | Depression resistant to conventional antidepressants |
| Turkoz 2021 | Post hoc analysis of the Transform study. |
| Vazquez 2021 | Does not meet eligibility criteria |
| Wajs 2020 | Depression resistant to conventional antidepressants |

Esketamine has a rapid mechanism of action and an often transient response. With a short follow-up time (28 days), evaluated in this review, it is not possible to extrapolate, in the long term, the result obtained from the treatment of severe depressive illness with resistance to ADO, which is often chronic, demanding treatment for long and indeterminate periods.

As limitations of this study, first, we can mention the number of the tested population, which is relatively small and may lead to publication bias. According to the evaluation through the questionnaire (MARDS), with results in mean and SD, it may not reflect a categorical improvement in absolute and individual terms of these patients.

## CONCLUSION

The use of esketamine and *standard of care* compared to placebo and *standard of care,* in patients with resistant depression, reduces baseline MADRS and increases the number of patients with ≥50% reduction MADRS initial as well as remission (MADRS score≤12), in a period of up to 28 days, in patients with ADO-resistant depression. Esketamine is shown to be safe, without increasing serious adverse events.

Therefore, it is concluded that patients with ADO-resistant depression benefit from the use of esketamine 28–84 mg, nasal *spray,* twice a week, for 4 weeks, associated with oral antidepressants.

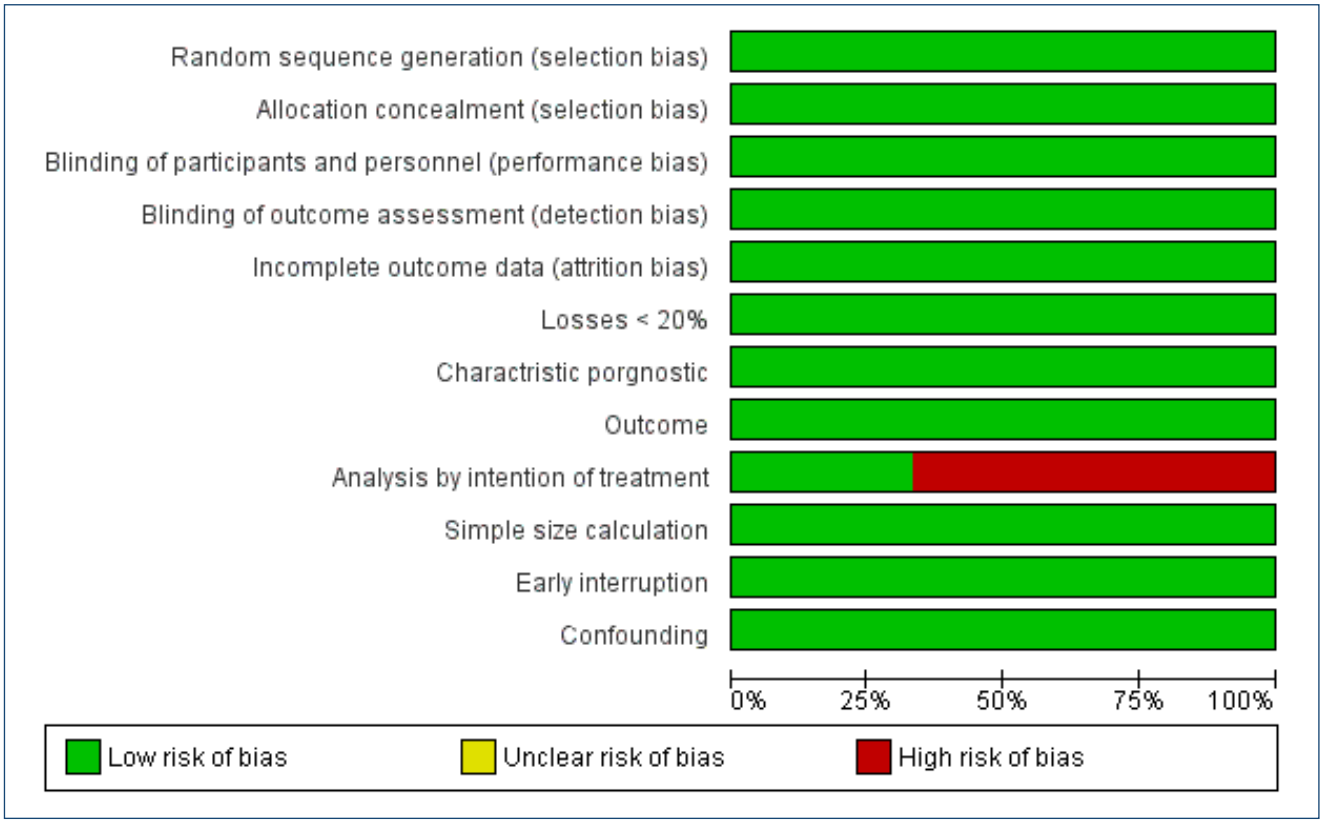


**Figure 2.** Risk of bias (red=presence; green=absence; and yellow=risk of unclear bias).

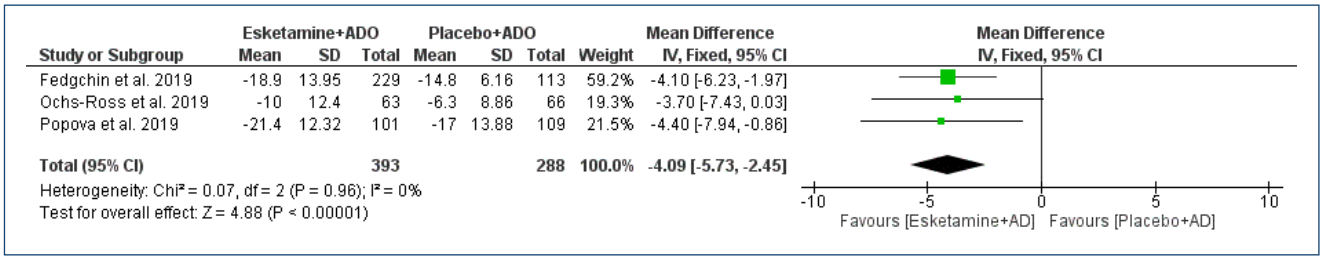


**Figure 3.** Meta-analysis of the mean reduction in Montgomery-Asberg Depression Rating Scale.

**Table 3.** Quality of evidence (GRADE).

| **Summary of findings:** | | | | | |
|---|---|---|---|---|---|
| **Evaluate the efficacy and safety of using esketamine and AD in elderly participants with treatment-resistant depression compared to placebo for treatment-resistant depression.** | | | | | |
| **Patient or population:** Patients with treatment-resistant depression<br>**Setting:**<br>**Intervention:** Evaluate the efficacy and safety of using esketamine and AD in participants with treatment-resistant depression.<br>**Comparison:** Placebo | | | | | |
| **Outcomes** | **Anticipated absolute effects* (95%CI)** | | **Relative effect (95%CI)** | **No. of participants (studies)** | **Certainty of the evidence (GRADE)** |
| | **Risk with placebo** | **Risk with esketamine** | | | |
| Mean change from baseline in MADRS total score up to endpoint | The mean change from baseline in MADRS total score up to endpoint was **0** | MD **4.09 lower** (5.73 lower to 2.45 lower) | – | 681 (3 RCTs) | ⊕⊕⊕O Moderate[a] |
| Participants in remission (MADRS£12) | 243 per 1,000 | **340 per 1,000** (267–430) | **RR 1.40** (1.10–1.77) | 703 (3 RCTs) | ⊕⊕⊕O Moderate[a,b] |
| Participants who achieved ³50% reduction from baseline in MADRS total score | 215 per 1,000 | **336 per 1,000** (265–428) | **RR 1.56** (1.23–1.99) | 703 (3 RCTs) | ⊕⊕⊕⊕ Moderate[b] |
| Adverse events serious | 17 per 1,000 | **27 per 1,000** (10–79) | **RR 1.58** (0.55–4.55) | 703 (3 RCTs) | ⊕OOO Very low[c] |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). CI: confidence interval; MD: mean difference; RR: risk ratio. GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be slightly different from the estimate of the effect. Very low certainty: We have very less confidence in the effect estimate: the true effect is likely to be slightly different from the estimate of effect. [a]Does not apply analysis by the intent of treatment. [b]Wide confidence interval. [c]Confidence interval crosses the nullity line.

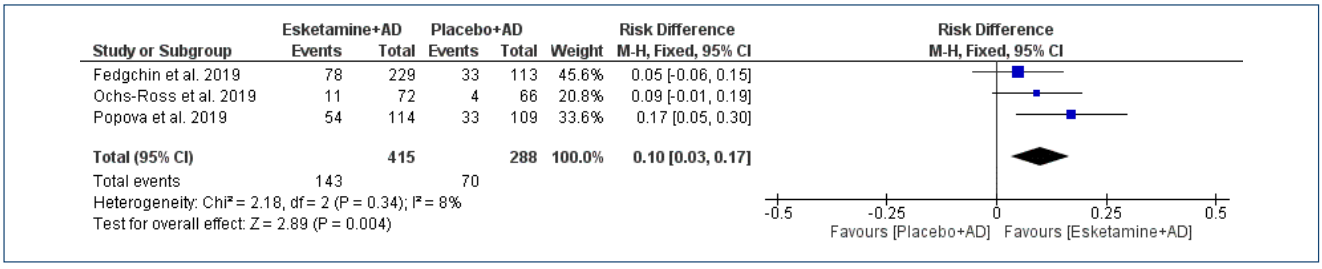


**Figure 4.** Meta-analysis of the "remission" rate (reduction to ≤12 points on the Montgomery-Asberg Depression Rating Scale), fixed effect.

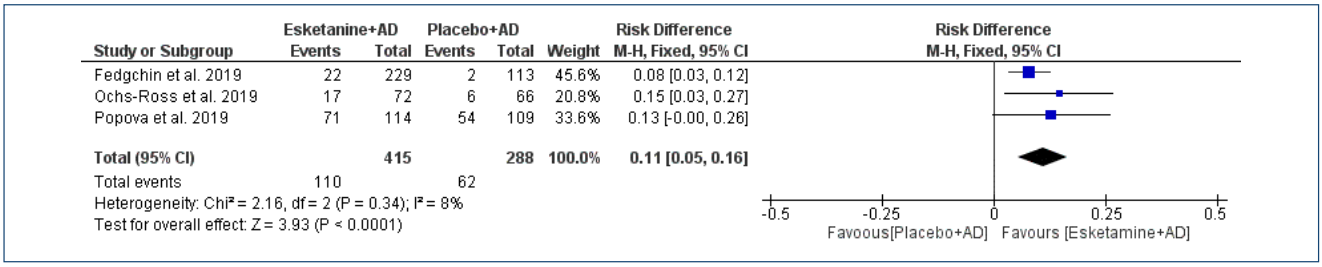


**Figure 5.** Meta-analysis of the rate of patients with a ≥50% reduction in Montgomery-Asberg Depression Rating Scale, fixed effect.

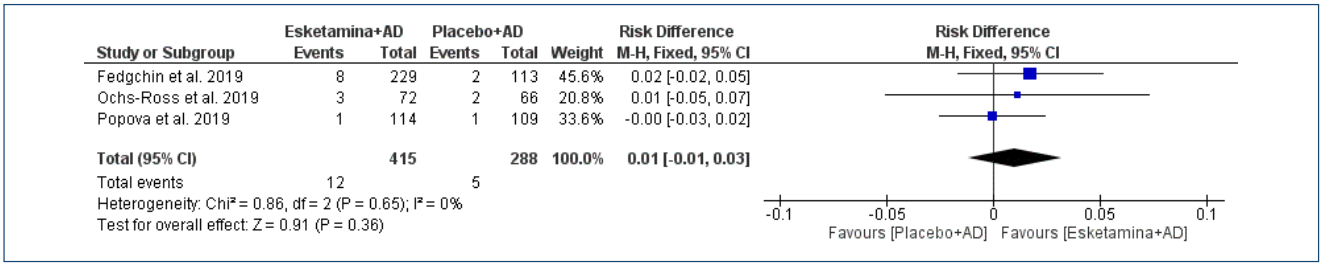


**Figure 6.** Meta-analysis of serious events, fixed effect.

## 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.

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