Meta-analytic evidence on esketamine in major depressive disorder: An umbrella review

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SUMMARY

Esketamine is a glutamatergic treatment option for major depressive disorder, particularly treatment-resistant depression, because of its rapid antidepressant effects. However, the expanding meta-analytic literature is characterized by methodological heterogeneity and partial overlap of primary trials, which complicates the clinical interpretation of efficacy and safety findings. A higher-level synthesis is therefore needed to contextualize the existing evidence.

We conducted an umbrella review of published meta-analyses evaluating the efficacy and/or safety of esketamine in adults with MDD. PubMed/MEDLINE and Scopus were searched for meta-analyses published between December 2020 and December 2025. Given overlap of primary trials and heterogeneity in outcome definitions, findings were synthesized qualitatively. Outcomes included depressive symptom severity, response and remission rates, suicidality-related outcomes, relapse and maintenance effects, and safety and tolerability.

Twenty-nine meta-analyses were included. Esketamine was associated with reductions in depressive symptom severity compared with placebo, with effects most pronounced at very early post-administration time points (hours to days). Reported effect sizes were generally small to moderate. Response and remission rates were higher in the acute phase, particularly at early assessments. Outcomes related to suicidal ideation were examined in a limited number of meta-analyses and were largely confined to acute post-dose evaluations. Relapse prevention and maintenance effects were reported in few meta-analyses and were mainly based on similar continuation-phase trials. Esketamine was associated with higher rates of non-serious adverse events, most commonly dissociation, dizziness, sedation, and gastrointestinal symptoms, while serious adverse events and all-cause discontinuation were not consistently increased.

At the meta-analytic level, intranasal esketamine is associated with a rapid-onset antidepressant effect of modest magnitude that appears time-sensitive. Current evidence suggests that esketamine may be considered as an adjunctive option for early symptomatic relief in selected patients. However, evidence regarding long-term effectiveness, relapse prevention, and effects on suicidal ideation remains limited. Further independently funded studies with long-term outcomes are needed to better define its clinical role.

Key Words: Esketamine, Intranasal Administration, Major Depressive Disorder, Meta-Analysis, Suicidal Ideation, Treatment-Resistant Depression

INTRODUCTION

Treatment-resistant depression (TRD) refers to patients with major depressive disorder (MDD) who remain symptomatic after two or more antidepressant trials administered at adequate doses and for sufficient durations. The clinical relevance of this population is substantial, as TRD has been linked to a an increased risk of suicide, a recurrent course, marked functional impairment, and greater utilization of healthcare services. Population-based studies indicate that approximately 20–30% of individuals with depression meet criteria for treatment resistance (1,2). Accordingly, TRD represents a major area of unmet need in clinical psychiatry.

Pharmacological treatments for depression have historically been grounded in the modulation of monoaminergic systems, including serotonin, noradrenaline, and dopamine. However, persistently

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low rates of full remission and high risks of relapse suggest that the biological underpinnings of depression extend beyond monoaminergic dysfunction alone (3, 4). In recent years, a broader neurobiological framework has been proposed, incorporating mechanisms related to synaptic plasticity, glutamatergic dysregulation, neuroinflammation, and alterations in stress-response systems (2,4). These developments have stimulated increasing interest in novel, non-monoaminergic therapeutic targets for depression.

Within this context, treatments targeting glutamatergic modulation have emerged as particularly promising options in the management of TRD. Esketamine, the S-enantiomer of ketamine that acts as an N-methyl-D-aspartate (NMDA) receptor antagonist, has gained clinical and scientific attention because of its rapid antidepressant effects and its role in modulating synaptic plasticity. Randomized controlled trials (RCTs) and subsequent meta-analytic evaluations have demonstrated that esketamine can produce relatively early-onset antidepressant effects in patients with depression (5-7). Despite accumulating meta-analytic evidence, uncertainty persists regarding the magnitude, temporal persistence, and clinical significance of esketamine's effects, supporting the need for a higher-level synthesis. Moreover, safety and tolerability outcomes related to esketamine treatment have been reported inconsistently across meta-analyses, reflecting heterogeneity in adverse event reporting across the meta-analytic literature. Uncertainty therefore remains regarding the consistency and clinical interpretation of safety findings.

Given the rapidly expanding and partially overlapping meta-analytic literature on esketamine, a higher-level synthesis is needed to clarify the consistency, magnitude, and clinical relevance of its reported effects.

The aim of this umbrella review is therefore to synthesize and critically appraise evidence reported in published meta-analyses evaluating the clinical effectiveness and safety profile of esketamine for depressive disorders. Specifically, meta-analytic findings relating to depressive symptom severity, response and remission rates, acute effects on suicidal ideation, relapse and maintenance outcomes, and safety and tolerability profiles are comparatively examined within a unified analytical framework.

METHOD

This study uses an umbrella review approach and follows PRISMA reporting principles for systematic reviews and meta-analyses. The objective of this umbrella review was to synthesize evidence from published quantitative meta-analyses examining the therapeutic effectiveness and safety outcomes of esketamine in major depressive disorder (MDD), including treatment-resistant depression (TRD) and depressive episodes accompanied by acute suicidal ideation. A PRISMA flow diagram was used to illustrate the study selection process.

Search Strategy

Eligible meta-analyses published between December 2020 and December 2025 were identified through structured searches of the PubMed/MEDLINE and Scopus databases. Searches were restricted to English-language publications. Keyword combinations addressing esketamine and depressive disorders were applied in the database searches, as outlined below:

(esketamine OR "S-ketamine" OR "Spravato" OR "intranasal esketamine") AND ("major depressive disorder" OR depression OR "treatment-resistant depression" OR TRD) AND (meta-analysis).

Reference lists of relevant publications were also reviewed, and additional focused searches were undertaken to capture any further eligible studies.

Eligibility Criteria

Meta-analyses were included if they:

- Involved adult populations with MDD or TRD,
- Evaluated esketamine treatment for efficacy

and/or safety outcomes, and

• Reported quantitative pooled estimates comparing esketamine with placebo and/or standard antidepressant treatments.

Studies were excluded if they met any of the following criteria:

• Conducted in pediatric populations

• Reported pharmacokinetic data exclusively

• Assessed racemic ketamine without providing esketamine-specific analyses

Study Selection and Data Extraction

An initial screening of titles and abstracts was performed independently by two investigators to identify potentially relevant records. Full texts were then examined for eligibility, with any unresolved differences adjudicated by a third reviewer.

Relevant data were collected using a predefined extraction framework and included publication characteristics, number of included trials and participants, treatment and comparator arms, outcome domains (depressive symptom severity, response and remission, relapse/maintenance outcomes, suicidal ideation, and safety/tolerability), effect size metrics (SMD, MD, OR, RR, or HR), heterogeneity estimates (I^2), subgroup analyses, and reported funding sources or conflicts of interest. For heterogeneity estimates, a uniform classification was applied to enhance interpretability across meta-analyses and does not imply re-analysis of original pooled estimates. Effect estimates were extracted and presented according to the original coding and directionality used in each meta-analysis and were not re-coded for standardization.

Evaluation of Methodological Quality and Evidence Synthesis

Two reviewers independently evaluated the methodological rigor of the included meta-analyses with the AMSTAR-2 tool. Given the methodological heterogeneity, overlap of primary trials, and variability in outcome definitions across meta-analyses, no additional quantitative pooling was performed. Instead, findings were synthesized qualitatively and thematically, drawing on the results reported across the selected meta-analyses.

To ensure comparability across meta-analyses, heterogeneity was interpreted using a predefined, uniform classification based on Cochrane guidance, irrespective of the thresholds applied in individual studies. I^2 values $<40\%$ were considered low, 40–60% moderate, and $>60\%$ high heterogeneity. The synthesis focused on a comparative evaluation of evidence across meta-analyses to characterize the efficacy, temporal profile, relapse/maintenance outcomes, and safety–tolerability of esketamine in depression.

Overlap Assessment

To quantify the degree of overlap among the included meta-analyses and to address the potential risk of double counting of primary studies, we constructed a citation matrix and calculated the Corrected Covered Area (CCA). The citation matrix mapped the occurrence of each primary randomized controlled trial across the included meta-analyses. The CCA was calculated using the formula $CCA=(N-r)/(rc-r)CCA=(N-r)/(rc-r)$, where N represents the total number of occurrences of primary studies across reviews, r the number of unique primary studies, and c the number of reviews included in the umbrella review.

Certainty of evidence assessment

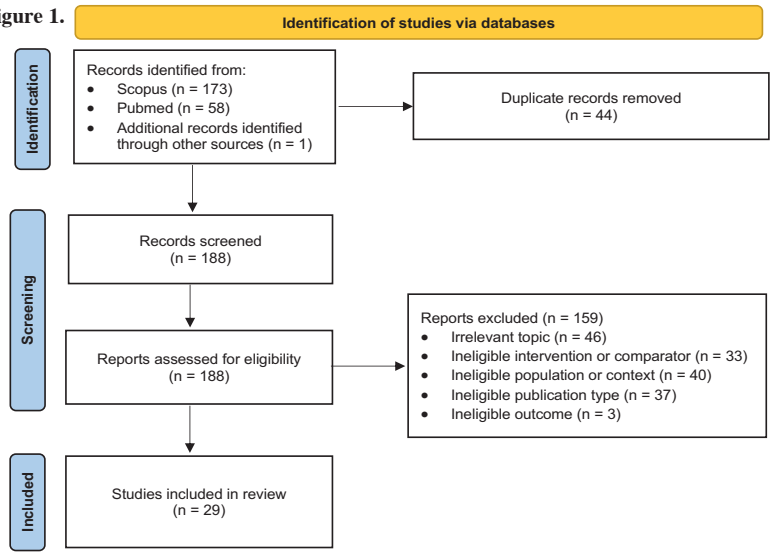
Certainty of evidence for the main outcome domains was evaluated using the GRADE approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

RESULTS

Overview of included meta-analyses

A total of 29 meta-analyses were identified through

Figure 1.



the literature search and included in the final synthesis (Figure 1). All included meta-analyses synthesized data from randomized controlled trials and primarily involved samples diagnosed with major depressive disorder (MDD), with several analyses focusing specifically on treatment-resistant depression (TRD) or mixed MDD populations (Table 1).

Across meta-analyses, primary efficacy outcomes most commonly reflected changes in depressive symptom severity, assessed using validated rating scales. The Montgomery–Åsberg Depression Rating Scale (MADRS) was the most frequently employed outcome measure, while some meta-analyses also reported outcomes based on the Hamilton Depression Rating Scale (HAM-D/HDRS) or standardized derivatives of these instruments. Effect sizes were reported using standardized mean differences (SMD), mean differences (MD), Hedges' g, or Cohen's d.

Response and remission rates were frequently evaluated as secondary or co-primary endpoints, typically expressed using odds ratios (OR), risk ratios (RR), or risk differences (RD). A smaller subset of meta-analyses, particularly those incorporating continuation or longitudinal follow-up data, assessed relapse or recurrence risk, most often reported using hazard ratios (HR).

Suicidality-related outcomes were reported heterogeneously across meta-analyses. Some studies assessed acute changes in suicidal ideation using specific instruments (e.g., MADRS-SI, C-SSRS, or comparable scales), whereas others did not report suicidality-related outcomes or addressed them only as secondary or exploratory analyses. Safety and tolerability outcomes commonly included adverse events (AEs), serious adverse events (SAEs), and treatment discontinuation. In several studies, discontinuation due to adverse events and all-cause dropout rates were evaluated alongside efficacy outcomes, although the scope, selected safety endpoints, reporting formats, and duration of follow-up varied across meta-analyses.

With respect to route of administration, the majority of included meta-analyses focused on intranasal esketamine, while a limited number incorporated studies evaluating intravenous esketamine. Esketamine was evaluated as adjunctive therapy in some meta-analyses, while others examined monotherapy or both treatment approaches. Several meta-analyses also included direct, indirect, or network-based comparisons of esketamine with active treatments such as intravenous ketamine or second-generation antipsychotic augmentation.

Sample sizes varied considerably across meta-analyses, and because of substantial overlap of primary trials, calculation of a unique pooled patient population was not feasible. A substantial proportion of meta-analyses included industry-sponsored trials or reported limited information on conflicts of interest.

Table 1. Meta-Analyses of Esketamine on Efficacy, Safety, and Suicidality

#	Author (Year)	Included Studies	Total Sample Size	Treatment	Comparator	Primary Outcome Measures	Effect Size	Heterogeneity[a]	Conflict Of Interest[b]
1	Fountoulakis et al. (2025) (8)	11 RCTs (10 acute, 1 maintenance)	1,774 (acute: 959 IN ESK, 785 placebo; 20 IV ESK, 10 placebo; maintenance: 297 ESK)	IN/IV ESK + AD	Placebo + AD	MADRS; CGI-SS-r; BSSI; C-SSRS	SMD (MADRS): 24 h: -0.33 (-0.43 to -0.24) 1 week: 0.25 (-0.34 to -0.16) 2 weeks: -0.15 (-0.27 to -0.04) 4 weeks: -0.23 (-0.32 to -0.13) Suicidality: No significant effect demonstrated	Low□moderate (I†: 0□53%)	NR
2	Wang et al. (2023) (20)	12 RCTs (overall network; 2 ESK RCTs)	4,276 (343 ESK, 22 placebo)	IN ESK + AD	Placebo + AD	MADRS; response rate	MADRS: MD = -4.24 (-7.12 to -1.37; p = 0.0038) Response rate difference: 25%, p < 0.0001	NR (ESK-specific)	Industry-funded
3	Naudet et al. (2025) (15)	7 RCTs (6 acute, 1 maintenance)	1,505 (873 ESK, 692 placebo)	IN ESK + AD	Placebo + AD	MADRS; relapse risk (HR)	MADRS (acute): MD = -2.94 (95% CI -5.39 to -0.48) Relapse risk (maintenance): HR = 0.38 (0.26□0.57)	MADRS: Low□ moderate (I† = 28%) Relapse risk: NR	NR
4	Dold et al. (2020) (21)	25 RCTs (3 ESK RCTs)	9,004 (373 ESK, 268 placebo)	IN ESK + AD	Placebo + AD	MADRS	MADRS: MD = 4.09 (95% CI 2.01□6.17)	Moderate (I† = 43.9%)	No external funding; conflicts of interest declared (industry relationships)
5	VÆzquez et al. (2021) (17)	49 RCTs (7 ESK RCTs)	10,031 (711 ESK, 576 placebo)	IN ESK + AD	Placebo + AD	Response rate (MADRS/HDRS)	Response: OR = 1.96 (95% CI 1.55□2.50)	Low (I† < 1%)	No conflicts of interest declared
6	Seshadri et al. (2024) (26)	12 RCTs (7 IN ESK, 1 IV ESK RCTs)	1,549 (730 IN ESK, 557 placebo; 20 IV ESK, 10 placebo)	IN/IV ESK + AD	Placebo + AD	MADRS	IN esketamine: Hedges□ g = 0.31 (95% CI 0.180.44; p < 0.001)	Low (I† = 22%)	No conflicts of interest declared
7	Gowthami et al. (2025) (19)	17 RCTs	10,073 (5,707 ESK, 4,622 placebo)	IN ESK + AD	Placebo + AD	MADRS; response; remission	MADRS: MD = -1.47 (-3.01 to 0.07; p = 0.06) Response: OR = 0.51 (0.30□0.73; p < 0.001)[c] Remission: OR = 0.35 (0.11□0.58; p < 0.001)[c]	MADRS: high (I† = 99.2%) Response: high (I† = 79.7%) Remission: high (I† = 75.5%)	Industry-sponsored trials included
8	Nikolin et al. (2023) (24)	49 RCTs (9 IN ESK, 1 IV ESK RCTs)	3,299 (959 IN ESK, 783 placebo; 20 IV ESK, 10 placebo)	IN/IV ESK + AD	Placebo + AD	MADRS/HDRS; response; remission; all-cause drop-out	MADRS/HDRS □Acute (single dose): Low dose: SMD = -0.55 (-0.87 to -0.24; p = 0.0006) High dose: SMD = -0.48 (-0.75 to -0.20; p = 0.0007) Repeated dosing: Low dose: SMD = -0.15 (-0.49 to 0.19; p = 0.40) High dose: SMD = -0.22 (-0.54 to 0.10; p = 0.18) Follow-up: SMD = -0.33 (-0.96 to 0.31; p = 0.31) Response: OR = 1.76 (95% CI 0.89□3.49; p = 0.10) Remission: OR = 1.80 (95% CI 1.14□2.82; p = 0.011) All-cause drop-outs:Low dose: OR = 1.06 (0.48□2.34; p = 0.88) High dose: OR = 1.20 (0.83□1.74; p = 0.33)	MADRS: Acute: high (I† = 60.5%) Repeated dosing: very high (I† = 84.2%) Follow-up: high (I† = 87.6%) Response / Remission / All-cause drop-outs: NR (ESK-specific)	Industry-sponsored trials included
9	Floriano et al. (2023) (14)	3 RCTs	703 (415 ESK, 288 placebo)	IN ESK + AD	Placebo + AD	MADRS; response; remission; serious adverse events	MADRS: MD = -4.09 (95% CI -5.73 to -2.45; p=0.00001) Response: RD = 0.11 (0.05□0.16; p=0.0001) Remission: RD = 0.10 (0.03□0.17; p=0.004) SAEs: RD = 0.01 (-0.01 to 0.03; p=0.36)	MADRS: low (I† = 0%) Response: Low (I† = 8%) Remission: Low (I† = 8%) SAEs: low (I† = 8%)	No conflicts of interest declared
10	Ouyang & Li (2025) (25)	5 RCTs	1,315 (464 ESK, 465 placebo)	IN ESK + AD	Placebo + AD	MADRS; response; remission	MADRS: SMD = -3.88 (95% CI -5.71 to -2.05; p < 0.0001) (very large effect size) Response: RR = 1.99 (95% CI 1.28□3.10; p = 0.002) Remission: RR = 1.50 (95% CI 0.91□2.49; p = 0.11)	MADRS: low (I† = 0%) Response: low (I† = 0%) Remission: low (I† = 29%)	No conflicts of interest declared
11	CALDER ET AL. (2024) (12)	19 RCTS (4 IN ESK, 1 IV ESK RCTS)	2,042	IN/IV ESK + AD; 1 IN ESK (MONOTHERAPHY)	PLACEBO + AD	RESPONSE; DROPOUTS (ALL-CAUSE)	RESPONSE:1□3 DAYS: NNT = 2 (K = 1)WEEK 4: NNT = 11 (K = 4) DROP-OUTS:1□3 DAYS: NNH = -47 WEEK 4: NNH = 3 (K = 4)	NR	No external funding; conflicts of interest declared
12	Wang et al. (2021) (10)	8 RCTs	1,488 (719 ESK, 719 placebo)	IN ESK + AD	Placebo + AD	MADRS; remission; suicidality	MADRS □MDD: 2□4 h: SMD = -0.41 (95% CI -0.58 to -0.25; p < 0.00001) 24 h: SMD = -0.36 (95% CI -0.47 to -0.24; p < 0.00001) 1 week: SMD = -0.25 (95% CI -0.36 to -0.13; p < 0.0001) 3□4 weeks: SMD = -0.25 (95% CI -0.35 to -0.14; p < 0.00001) MADRS □TRD: 2□4 h: SMD = -0.67 (95% CI -1.16 to -0.17; p = 0.008) 24 h: SMD = -0.48 (95% CI -0.82 to -0.13; p = 0.007) 1 week: SMD = -0.27 (95% CI -0.42 to -0.12; p = 0.0003) 3 □4 weeks: SMD = -0.23 (95% CI -0.37 to -0.10; p = 0.0007) MADRS □MDSI: 2□4 h: SMD = -0.38 (95% CI -0.56 to -0.21; p < 0.0001) 24 h: SMD = -0.34 (95% CI -0.52 to -0.17; p = 0.0001) 1 week: SMD = -0.21 (95% CI -0.39 to -0.02; p = 0.03) 3 □4 weeks: SMD = -0.27 (95% CI -0.44 to -0.10; p = 0.002) Remission: 2□4 h: OR = 2.43 (95% CI 1.27□4.67; p = 0.007) Day 8: OR = 1.46 (95% CI 0.96□2.23; p = 0.08) Weeks 3□4: OR = 1.64 (95% CI 1.30□2.07; p < 0.0001) Suicidality: 2□4 h: OR = 2.04 (95% CI 1.37□3.05; p = 0.0005) 24 h: OR = 1.15 (95% CI 0.80□1.65; p = 0.46) Weeks 3□4: OR = 1.32 (95% CI 0.91□1.90; p = 0.44)	MADRS □MDD: low-moderate (I† = 0-42%) MADRS □TRD: high at 24 h (I† = 73%); no significant heterogeneity for other time points MADRS □MDSI: low (I† = 0) for all time poins Remission: low-moderate (I† = 0-41%) Suicidality: low (I† = 0%)	No conflicts of interest declared
13	Jawad et al. (2022) (13)	7 RCTs	1,427 (798 IN ESK, 623 placebo)	IN ESK + AD	IN placebo + AD	MADRS; response; remission; relapse prevention	MADRS: d = -0.239 (95% CI -0.335 to -0.142; p < 0.0001) Response: RR = 1.221 (95% CI 1.055□1.428; p = 0.017) Remission: RR = 1.366 (95% CI 1.182□1.578; p < 0.0001) Relapse prevention: Remitters: HR = 0.49 (95% CI 0.29□0.84) Responders: HR = 0.30 (95% CI 0.16□0.55)	MADRS: moderate (I† = 57%) Response / Remission / Relapse: NR (ESK-specific)	No external funding; conflicts of interest declared
14	Liu et al. (2022) (18)	7 RCTs	1,252 (701 ESK, 551 placebo)	IN ESK + AD	Placebo + AD	MADRS; response; remission; SDS	MADRS: MD = -2.68 (95% CI -3.98 to -1.37; p < 0.0001) SDS: MD = -2.90 (95% CI -4.01 to -1.79; p < 0.00001) Response: RR = 1.28 (95% CI 1.12□1.46; p = 0.0002) Remission: RR = 1.39 (95% CI 1.18□1.63; p < 0.0001) 24 h remission: RR = 1.96 (95% CI 1.29□2.99; p = 0.002) Sustained effective response: RR = 1.76 (95% CI 0.88□3.53; p = 0.11 AEs: Vertigo (RR = 9.21, 95% CI 4.82□17.57; p < 0.00001); dissociation (RR = 5.57, 95% CI 3.92□7.91; p < 0.00001); hypoesthesia (RR = 5.32, 95% CI 2.86□9.91; p < 0.00001); sedation (RR = 5.07, 95% CI 2.45□10.49; p < 0.0001); euphoric mood (RR = 4.56, 95% CI 1.90□10.91; p = 0.0007); paresthesia (RR = 4.25, 95% CI 2.42□7.46; p < 0.00001); blood pressure increased (RR = 3.36, 95% CI 2.23□5.06; p < 0.00001); vomiting (RR = 3.35, 95% CI 2.02□5.54; p < 0.00001); dizziness (RR = 3.20, 95% CI 2.46□4.16; p < 0.00001); nausea (RR = 2.63, 95% CI 2.01□3.44; p < 0.00001); somnolence (RR = 1.82, 95% CI 1.37□2.41; p < 0.0001); headache and anxiety not significant.	MADRS: low (I† = 0) SDS: low (I† = 0) Response: low (I† = 0) Remission: low (I† = 0) 24 h remission: low (I† = 0%) Sustained effective response: low (I† = 31%) AEs: anxiety moderate (I† = 49%), others low (I† = 0-21%)	No conflicts of interest declared

Continued Table 1. Meta-Analyses of Esketamine on Efficacy, Safety, and Suicidality

15	BAHJI ET AL. (2021A) (7)	36 RCTS (7 IN ESK, 2 IV ESK RCTS)	2,903	IN/IV ESK – AD	PLACEBO/KETAMINE – AD	MADRS/HAM-D; RESPONSE; REMISSION	MADRS/HAM-D: D = -0.38 RESPONSE: RR = 1.20 (95% CI 0.96□1.49) REMISSION: RR = 1.28 (95% CI 1.11□1.47)	NR (ESK-SPECIFIC)	INDUSTRY-SPONSORED TRIALS INCLUDED; CONFLICTS OF INTEREST DECLARED
16	Hieronymus et al. (2025) (23)	17 RCTs (2 ESK RCTs)	4,960 (349 ESK, 224 placebo)	ESK + AD	Placebo + AD	MADRS; response; drop-out	MADRS: SMD = 0.30 (SEM 0.12; p < 0.05) Response: 52% (181/349) (descriptive) Drop-out: 12% (43/349) (descriptive)	NR	No external funding; conflicts of interest declared
17	Huang et al. (2025) (16)	67 RCTs (13 IN ESK, 5 IV ESK, 1 oral ESK in MDD RCTs)	11,553 (1,785 IN ESK, 1,281 placebo; 321 IV ESK, 374 placebo; 57 oral ESK, 54 placebo)	IN/IV/oral ESK + AD	Placebo + AD / ECT	MADRS/HAMD, remission; response	Overall: SMD = -0.36 (95% CI -0.49 to -0.24) Remission rate: RR = 1.41 (95% CI 1.27□1.57) Response rate: RR = 1.28 (95% CI 1.18□1.39)	NR	NR
18	Wang et al. (2025) (27)	9 RCTs	2,394	IN ESK + AD	Placebo + AD/quetiapine	MADRS; remission; response; relapse; MADRS-SI/C-SSRS	MDD with suicidal ideation □Day 2: MADRS: SMD = -0.30 (95% CI -0.47 to -0.12; p = 0.0008) Remission rate: RR = 1.87, 95%CI: 1.11□3.15, *P* = 0.0179) TRD without suicidal ideation □Day 28: MADRS: SMD = -0.24 (95% CI -0.38 to -0.09; p = 0.001) All population: Remission (Day 28): RR = 1.36 (95% CI 1.18□1.57; p < 0.0001) Response (Day 28): RR = 1.20 (95% CI 0.99□1.46; p = 0.0630) Relapse: RR = 0.60 (95% CI 0.45□0.80, p < 0.05) Suicidal ideation: RR = 0.83 (95% CI 0.55□1.24; p = 0.3593) Drop-out (side effects): RR = 2.20 (95% CI 1.27□3.80; p = 0.0047) AEs: Sedation (RR = 4.55, 95% CI 2.20□9.38; p < 0.0001); somnolence (RR = 1.81, 95% CI 1.36□2.39; p < 0.0001); dissociation (RR = 4.54, 95% CI 2.36□8.73; p < 0.00001); dizziness (RR = 3.00, 95% CI 1.80□5.00; p < 0.0001); mental impairment and blood pressure increase not significant.	MDD with suicidal ideation □Day 2: MADRS: low (I† = 0) Remission rate: low (I† = 0) TRD without suicidal ideation □Day 28: MADRS: low (I† = 24) All population: Remission (Day 28): low (I† = 0%) Response (Day 28): moderate (I† = 51%) Relapse: low (I† = 0%) Suicidal ideation: low (I† = 0%) Drop-out (side effects): low (I† = 0%) AEs: BP: high (I† = 72%), others low (I† = 0%)	No conflicts of interest declared
19	Orace et al. (2024)[d] (11)	9 RCTs	1,752 (966 ESK, 786 placebo)	IN ESK + AD	Placebo + AD	Response; remission (MADRS)	Response: RR = 1.27 (95% CI 1.11□1.47, p = 0.001) Remission: RR = 1.37 (95% CI 1.19□1.57, p < 0.0001)	Response: low-moderate (I† = 0□58) Remission: low (I† = 0□12)	Industry-sponsored trials included
20	Papakostas et al. (2020) (6)	5 RCTs	774 (442 ESK, 332 placebo)	IN ESK + AD	Placebo + AD	MADRS; response; remission	MADRS: SMD = 0.36 (0.24□0.49; p < 0.0001) Response: RR = 1.40 (1.22□1.61; p < 0.0001) Remission: RR = 1.45 (1.20□1.75; p < 0.0001)	NR	No external funding; conflicts of interest declared
21	Hock et al. (2022) (9)	8 RCTs	1,437 (802 ESK, 635 placebo)	IN ESK + AD	Placebo + AD	MADRS; remission	MADRS:24 h: SMD = 0.34 (0.11□0.46; p < 0.0001) Endpoint: SMD = 0.26 (0.16□0.37; p = 0.004) Remission: 24 h: RR = 2.31 Endpoint: RR = 1.37	NR	No external funding; conflicts of interest declared
22	Terao et al. (2024) (32)	22 RCTs (5 ESK RCTs)	2,031 (626 ESK, 461 placebo)	IN ESK + AD	Placebo + AD	Response (MADRS/HAMD); drop-outs (due to side effects and all reasons)	Response: OR = 1.67 (1.19□2.33) Drop-out (side effects): OR = 3.03 (1.41□6.53) Drop-out (all reasons): OR = 1.25 (0.82□1.90)	NR (ESK-specific)	No conflicts of interest declared
23	Bahji et al. (2021b) (28)	24 RCTs (7 IN ESK, 1 IV ESK RCTs)	1,877 (1,097 IN ESK+placebo; 40 IV ESK+placebo)	IN/IV ESK + AD	Placebo + AD; ketamine	MADRS/HDRS; response; remission; adverse events; discontinuation; suicidality	MADRS/HDRS: SMD = -1.19 (-1.75 to -0.63) Response: RR = 1.38 (1.06□1.79) Remission: RR = 1.47 (1.12□1.94) Adverse events: RR = 3.02 (1.34□6.79) Discontinuation: RR = 1.36 (0.91□2.03) Suicidality: SMD = 0.05 (-0.44 to 0.53)	MADRS/HDRS: high (I† = 94%) Response: moderate-high (I† = 58%) Remission: low (I† = 38%) AEs / Discontinuation / Suicidality: NR (ESK-specific)	Industry-sponsored trials included; conflicts of interest declared
24	Guo et al. (2024) (29)	72 RCTs (11 IN ESK, 1 IV ESK RCTs)	12,105 (1770 IN ESK, 1396 placebo/ketiapin; 34 IV ESK, 29 ketamin)	IN/IV ESK + AD	Placebo/ketamin/ketiapin + *AD*	Response and remission (MADRS); tolerability; safety	Response rate: OR = 2.90 (1.81□4.64) Remission rate: OR = 2.00 (1.44□2.78) Tolerability: OR = 3.10 (1.89□5.08) Safety: OR = 1.30 (0.71□2.37)	NR (ESK-specific)	NR
25	Wang et al. (2024) (35)	5 RCTs (1 ESK RCT)	391 (111 ESK, 72 placebo)	IN ESK + AD	Placebo + AD	MADRS; MADRS-SI	Esketamine-specific pooled estimate not available	NA	No external funding; industry-sponsored trials included
26	Li et al. (2025) (36)	13 RCTs (3 IN ESK, 1 IV ESK RCTs)	1,109 (521 IN ESK + placebo; 59 IV ESK + placebo)	IN/IV ESK	Placebo	CGI-SS; remission rate of SI; MADRS-SI	Not pooled (different SI assessment tools)	NA	No external funding; industry-sponsored trials included
27	Chen et al. (2023) (22)	17 RCTs (3 ESK RCTs)	1,224 (517 ESK)	IN ESK	Placebo	BSS; BHS; MADRS	Suicidality: 4□6 h: SMD = 0.26 (95% CI 0.09□0.44) 24 h: SMD = 0.30 (95% CI 0.13□0.47)	NR (ESK-specific)	NR
28	Guo et al. (2025) (31)	47 RCTs (14 ESK RCTs)	5,046 (number of ESK participants not specified)	IN/IV ESK +/- AD	Placebo +/- AD	Dropout (due to AEs); incidence of AEs and SAEs	Dropout: RR = 1.85 (95% CI 1.01□3.40); p = 0.05 Any AEs: RR = 1.35 (95% CI 1.22□1.49); p < 0.00001 SAEs: RR = 1.14 (95% CI 0.74□1.73); p = 0.56	Dropout: moderate (I† = 53%) Any AEs: high (I† = 78%) SAEs: low (I† = 0%)	Industry-sponsored trials included
29	Yang et al. (2022) (30)	4 RCTs (3 IN ESK, 1 IV ESK RCTs)	551	IN/IV ESK	Placebo	AEs	Dissociation (RR = 4.54, 95% CI 2.36□8.73; p < 0.00001); dizziness (RR = 3.00, 95% CI 1.80□5.00; p < 0.0001); vertigo (RR = 7.47, 95% CI 2.55□21.86; p = 0.0002); somnolence (RR = 1.73, 95% CI 1.02□2.95; p = 0.04); nausea (RR = 2.34, 95% CI 1.04□5.25; p = 0.04); headache and dysgeusia not significant.	Low (I† = 0%)	NR

AD, antidepressant; AE, adverse event; CGI-SS, Clinical Global Impression□Severity of Suicidality; C-SSRS, Columbia□Suicide Severity Rating Scale; ESK, esketamine; HAM-D/HDRS, Hamilton Depression Rating Scale; HR, hazard ratio; IN, intranasal; IV, intravenous; MADRS, Montgomery□sberg Depression Rating Scale; MADRS -SI, Montgomery□sberg Depression Rating Scale □Suicidal Ideation item; MD, mean difference; NNH, number needed to harm; NNT, number needed to treat; NR, not reported; OR, odds ratio; RCT, randomized controlled trial; RD, risk difference; RR, risk ratio; SAE, serious adverse event; SDS, Sheehan Disability Scale; SMD, standardized mean difference.
[a]Heterogeneity interpretation followed Cochrane thresholds: low (I† <40%), moderate (40□60%), high (>60%).
[b]Conflict of interest categories were standardized based on authors□ declarations and funding statements; no reclassification of original disclosures was performed.
[c]Effect estimates <1 reflect reverse coding (non-response/non-remission as outcome); direction favors esketamine.
[d]Dose-specific subgroup analyses were reported in this meta-analysis but are not shown here; only overall pooled estimates are presented for consistency.

Methodological quality of included meta-analyses

The methodological quality of the included meta-analyses, assessed with AMSTAR-2, was generally limited. Of the 29 included studies, 20 were rated as critically low, 7 as low, and 2 as high confidence. Item-level assessment showed that several key methodological weaknesses were recurrent across reviews, particularly the lack of justification for included study designs, failure to provide a list of excluded studies, limited reporting of funding sources for included primary studies, and inadequate consideration of risk of bias when interpreting pooled findings. The full AMSTAR-2 item-level assessment is presented in Supplementary Table 1.

Overlap of primary studies across meta-analyses

The citation matrix included 29 meta-analyses (c = 29) and 41 unique primary randomized controlled trials (r = 41), with 212 total occurrences of primary studies across reviews (N = 212). The calculated CCA was 0.149 (14.9%), indicating a high degree of overlap among the included meta-analyses. The citation matrix used for the CCA calculation is provided in Supplementary Table 2.

Efficacy on depressive symptom severity

The included meta-analyses indicated reductions in depressive symptom severity following esketamine administration, with some demonstrating early-onset effects within hours to days (8-10) and others, including analyses reporting both early and later acute outcomes, demonstrating short-term efficacy over acute treatment periods (6, 9, 11-18), generally with small-to-moderate effect sizes compared with placebo (Table 1).

Table 2. Certainty of evidence for main outcome domains according to the GRADE approach

Outcome Domain	Certainty of Evidence (GRADE)
Short-Term Depressive Symptom Reduction	Moderate
Response	Moderate
Remission	Low
Suicidality / Suicidal Ideation	Low
Relapse Prevention / Maintenance	Low
Non-Serious Adverse Events	Moderate
Serious Adverse Events	Low

Meta-analyses reporting absolute changes in symptom severity indicated that adjunctive intranasal esketamine was associated with mean improvements of approximately 1.5 to 4 MADRS points compared with placebo (14,15,18-21). Consistent with these findings, the majority of meta-analyses using standardized effect size metrics (SMD, Hedges' g, or Cohen's d) reported small-to-moderate effect sizes favoring esketamine (6-10, 13, 16, 22-27). A notably larger effect size was reported in a single subgroup meta-analysis by Bahji et al., however this estimate was accompanied by wide confidence intervals and substantial heterogeneity (28).

Meta-analyses examining the temporal profile of treatment effects generally indicated that antidepressant effects of intranasal esketamine may emerge within the first few hours following admin-

Supplementary Table 1. AMSTAR-2 assessment of the methodological quality of the included meta-analyses

AMSTAR	PICO	Protocol	Study Design Justified	Search Strategy	Selection Duplicate	Extraction Duplicate	Excluded Studies	Study Description	Risk of Bias	Meta-analysis Method	RoB in Interpretation	Hetero geneity	Publication Bias	Heterogeneity Discussion	Funding Reported	Conflict of Interest	Overall Confidence
Fountoulakis et al., 2025	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	Yes	Critically Low
Wang et al., 2023	Yes	No	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Naudet et al., 2025	Yes	Yes	No	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Dold et al., 2020	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
VÆzquez et al., 2021	Yes	No	No	Partial yes	Yes	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes	Critically Low
Seshadri et al., 2024	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Gowthami et al., 2025	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Critically Low
Nikolin et al., 2023	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Floriano et al., 2023	Yes	Yes	No	Partial yes	No	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Low
Ouyang & Li, 2025	Yes	No	No	Partial yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Critically Low
Calder et al., 2024	Yes	No	No	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	Critically Low
Wang et al., 2021	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Critically Low
Jawad et al., 2022	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Liu et al., 2022	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically Low
Bahji et al., 2021a	Yes	Yes	No	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Hieronymus et al., 2025	Yes	No	No	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	Yes	Critically Low
Huang et al., 2025	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically Low
Wang et al., 2025	Yes	Yes	No	Partial yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	High
Oraee et al., 2024	Yes	Yes	No	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Papakostas et al., 2020	Yes	No	No	Partial yes	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Hock et al., 2022	Yes	No	No	Partial yes	No	Yes	No	Yes	No	No	Yes	No	No	Yes	No	Yes	Critically Low
Terao et al., 2024	Yes	Yes	No	Yes	Yes	Partial yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	High
Bahji et al., 2021b	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Guo et al., 2024	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Critically Low
Wang et al., 2024	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Critically Low
Li et al., 2025	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Chen et al., 2023	Yes	Yes	No	Partial yes	Yes	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically Low
Guo et al., 2025	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Yang et al., 2022	Yes	No	No	Partial yes	No	No	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Critically Low

PICO: Population, Intervention, Comparator, Outcome; RoB: Risk of Bias

istration. Early symptom reductions were observed as early as 2–6 hours post-dose, with small-to-moderate standardized effect sizes reported across multiple syntheses (8-10,22). At 24 hours post-dose, antidepressant effects were still detectable but were generally modest, with small-to-moderate effect sizes reported across meta-analyses (9,10, 22). Effect sizes were generally larger at very early assessments and smaller at later acute time points (8,10,24).

In separate subgroup analyses, larger early antidepressant effects were reported in treatment-resistant depression populations at very early assessment windows (10). Independently, analyses examining administration patterns (single vs. repeated dosing) suggested that repeated dosing and later follow-up periods were associated with more modest or non-significant effects compared with early post-dose assessments (24).

Dose-related effects were examined in only one meta-analysis, in which antidepressant effects of intranasal esketamine did not demonstrate a clear dose–response pattern, with similar effect sizes observed across lower and higher dose ranges (24).

Across meta-analyses reporting heterogeneity for MADRS outcomes, I^2 values ranged from low to high (Table 1), with higher heterogeneity reported in several analyses (19,24,28).

Response and remission rates

Across the included meta-analyses, intranasal esketamine was associated with higher response and remission rates compared with placebo at acute assessment points (Table 1). Early response and remission benefits were most consistently observed at very early assessment time points across analyses, particularly within hours to days following administration. Only a small number of meta-analyses directly examined response and remission across multiple acute time points. In these analyses, later assessments tended to show smaller effect estimates compared with very early post-administration outcomes (10, 12). One meta-analysis reported significant improvements in response, remission, and 24-hour remission outcomes, whereas no significant difference was observed for sustained effective response assessed during follow-up (18).

Across meta-analyses, response and remission effect estimates were generally modest in magnitude, with variability across studies according to assessment timing and analytic methodology (6,10, 11,13,18).

Across meta-analyses reporting heterogeneity, I^2 values for response and remission outcomes were mostly low, although several analyses reported moderate or high heterogeneity (10,11,19,28).

Supplementary Table 2. Citation matrix of primary esketamine randomized controlled trials across the included meta-analyses used for the Corrected Covered Area (CCA) calculation.

Primary RCT	Fountoulakis et al., 2025	Wang et al., 2023	Naudet et al., 2025	Dold et al., 2020	VÆzquez et al., 2021	Seshadri et al., 2024	Gowthami et al., 2025	Nikolin et al., 2023	Floriano et al., 2023	Ouyang & Li, 2025	Calder et al., 2024	Wang et al., 2021	Jawad et al., 2022	Liu et al., 2022
Canuso et al., 2018	1	0	0	0	1	1	0	1	0	0	0	1	1	1
Singh et al., 2016	1	0	0	0	0	1	0	1	0	0	1	0	0	0
Fu et al., 2020	1	0	0	0	1	0	0	1	0	0	0	1	1	1
Ionescu et al., 2021	1	0	0	0	1	0	0	1	0	0	0	1	1	1
Daly et al., 2018	1	0	1	0	1	1	0	1	0	1	0	1	0	0
Fedgchin et al., 2019	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Ochs-Ross et al., 2020	1	0	1	1	1	1	0	1	1	1	1	1	1	1
Popova et al., 2019	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Takahashi et al., 2021	1	0	1	0	0	1	1	1	0	0	1	1	1	1
Chen et al., 2023	1	0	1	0	0	1	0	1	0	0	0	0	0	0
Jha et al., 2023	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Jones et al., 2022	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Daly et al., 2021	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Sliwa et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Morrison et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Reif et al., 2023	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Daly et al., 2019	1	0	1	0	0	0	1	0	0	1	0	0	0	0
Young et al., 2025	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Hough et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Citrome et al., 2020	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Jamieson et al., 2023	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Turkoz et al., 2021	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Vieta et al., 2025	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Correia-Melo et al., 2020	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Smith-Apeldooen et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dijkstra et al., 2022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Janik et al., 2025	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Jarventausta et al., 2013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Kosik-Gonzales et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ren et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Zeng et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Zhou et al., 2023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lapidus et al., 2014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ohnishi et al., 2022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vieira et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hong et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Doty et al., 2021	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Katz et al., 2021	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Kern et al., 2024	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Clemens et al., 2025	0	0	0	0	0	0	1	0	0	0	0	0	0	0
McIntyre et al., 2025	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Total primary studies per meta-analysis	11	2	7	3	7	8	17	10	3	5	5	8	7	7

Supplementary Table 2 (continued). Citation matrix of primary esketamine randomized controlled trials across the included meta-analyses used for the Corrected Covered Area (CCA) calculation.

Primary RCT	Bahji et al., 2021a	Hieronymus et al., 2025	Huang et al., 2025	Wang et al., 2025	Oraee et al., 2024	Papakostas et al., 2020	Hock et al., 2022	Terao et al., 2024	Bahji et al., 2021b	Guo et al., 2024	Wang et al., 2024	Li et al., 2025	Chen et al., 2023	Guo et al., 2025	Yang et al., 2022
Canuso et al., 2018	1	0	1	1	1	1	1	0	1	1	0	1	1	1	1
Singh et al., 2016	1	0	1	0	0	0	0	0	1	0	0	0	0	1	1
Fu et al., 2020	1	0	1	1	1	0	1	0	0	1	0	1	1	1	0
Ionescu et al., 2021	1	0	1	1	1	0	1	0	0	1	0	1	1	1	0
Daly et al., 2018	1	0	1	0	1	1	1	1	1	1	0	0	0	1	1
Fedgchin et al., 2019	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1
Ochs-Ross et al., 2020	1	0	1	1	1	1	1	0	1	1	0	0	0	1	0
Popova et al., 2019	1	1	1	1	1	1	1	1	1	1	0	0	0	1	0
Takahashi et al., 2021	0	0	1	1	1	0	1	1	0	1	0	0	0	1	0
Chen et al., 2023	0	0	1	0	1	0	0	1	0	0	0	0	0	1	0
Jha et al., 2023	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Jones et al., 2022	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Daly et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sliwa et al., 2024	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Morrison et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Reif et al., 2023	0	0	1	1	0	0	0	0	0	1	0	0	0	1	0
Daly et al., 2019	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0
Young et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hough et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Citrome et al., 2020	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Jamieson et al., 2023	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Turkoz et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vieta et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Correia-Melo et al., 2020	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0
Smith-Apeldooen et al., 2024	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0
Dijkstra et al., 2022	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Janik et al., 2025	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Jarventausta et al., 2013	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Kosik-Gonzales et al., 2025	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Ren et al., 2024	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Zeng et al., 2025	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Zhou et al., 2023	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Lapidus et al., 2014	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Ohnishi et al., 2022	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Vieira et al., 2021	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Hong et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Doty et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Katz et al., 2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Kern et al., 2024	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Clemens et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
McIntyre et al., 2025	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total primary studies per meta-analysis	9	2	19	9	9	5	8	5	8	12	1	4	3	14	4

Suicidality and suicidal ideation

Outcomes related to suicidality and suicidal ideation were evaluated in only a subset of the included meta-analyses, with substantial variation in assessment instruments and outcome definitions (Table 1) (8,10,22,27). Some syntheses reported suicidality as a secondary outcome or provided limited poolable evidence due to heterogeneity across assessment tools (8,22).

Meta-analyses focusing on the acute treatment phase reported early reductions in suicidal ideation within the first hours to 24 hours following administration in some analyses (2,18). Evidence beyond the acute window was sparse: Wang et al. (2021) reported statistically significant reductions in suicidal ideation at early time points, with differing statistical significance at the one-week assessment (10). By contrast, Wang et al. (2025), examining suicidal ideation as part of broader efficacy outcomes, found no statistically significant difference compared with placebo (27).

Heterogeneity reporting for suicidality-related outcomes was limited across the included meta-analyses; where reported, heterogeneity was low (10, 27), but most syntheses did not provide I^2 estimates, restricting cross-study comparisons. Importantly, suicidality was not examined as a primary, adequately powered endpoint in the included meta-analyses, and longer-term suicidal outcomes beyond the acute phase were typically assessed as secondary or exploratory measures.

Relapse and maintenance outcomes

Relapse and maintenance outcomes were examined in only a limited subset of the included meta-analyses and were reported using heterogeneous outcome measures (8,13,15,27). Naudet et al. assessed relapse risk during the maintenance phase using hazard ratios (HR) and reported a lower risk of relapse favoring esketamine (15). Jawad et al. evaluated relapse prevention separately in remitter and responder subgroups, reporting hazard ratios favoring esketamine in both populations (13). Wang et al. reported relapse outcomes using risk ratios (RR) and similarly found lower relapse rates in the esketamine groups compared with control conditions (27). Fountoulakis et al. examined maintenance and relapse-related outcomes across acute and continuation phases but reported these endpoints using heterogeneous definitions and a limited number of maintenance trials, precluding pooled estimates for relapse prevention (8).

Overall, evidence regarding relapse prevention and maintenance effects is derived from a limited number of meta-analyses and is characterized by heterogeneity in outcome definitions (e.g., hazard

ratios vs. risk ratios), follow-up duration, and patient subgroups examined (8,13,15,27). Across the included meta-analyses, relapse-related outcomes were generally reported in favor of esketamine during continuation or maintenance treatment, but these findings were largely based on overlapping data from a small number of maintenance-phase trials.

Safety and tolerability

Safety and tolerability outcomes were reported inconsistently across meta-analyses and included adverse events, serious adverse events, and discontinuation outcomes (Table 1).

Across meta-analyses, intranasal esketamine was generally associated with a higher frequency of adverse events, particularly non-serious adverse events, compared with placebo (18, 28-30). In three meta-analyses providing detailed adverse event profiles, esketamine was consistently associated with increased risks of dissociation or perceptual disturbances, dizziness or vertigo, somnolence or sedation, and nausea or vomiting. In contrast, headache and anxiety were not consistently increased across meta-analyses that reported these outcomes (18, 27, 30).

Findings related to serious adverse events were limited. Two meta-analyses reported pooled estimates for serious adverse events using different effect measures, and neither found a statistically significant difference in SAE rates between intranasal esketamine and placebo (14,31). These estimates were based on a small number of contributing trials and a low frequency of events.

Treatment discontinuation outcomes varied across meta-analyses depending on how dropout was defined. Evidence on all-cause discontinuation was limited and heterogeneous, with several meta-analyses reporting no statistically significant differences between intranasal esketamine and placebo (24, 32), while others provided only descriptive or time-dependent estimates without pooled comparisons (12, 23). In contrast, meta-analyses focusing on discontinuation due to adverse events generally reported higher discontinuation rates in the esketamine group, including a significant increase in dropout due to side effects (27,32) and a borderline increase in AE-related dropout risk (31), with directionally higher but non-significant estimates also reported elsewhere (28).

Where reported, heterogeneity for safety and tolerability outcomes ranged from negligible to high. Several analyses reported low or absent heterogeneity for serious adverse events and most non-specific adverse events, whereas higher heterogeneity was observed for outcomes such as overall adverse events, blood pressure–related adverse events, and anxiety-related measures (18,27,31).

Evidence certainty across outcome domains

Certainty of evidence was evaluated using the GRADE approach and is summarized in Table 2. Certainty was moderate for short-term depressive symptom reduction, response/remission, and non-serious adverse events, low for relapse prevention and serious adverse events, and very low for suicidality-related outcomes.

DISCUSSION

This umbrella review synthesizes meta-analytic evidence on the efficacy, safety, and tolerability of intranasal esketamine in major depressive disorder (MDD), including meta-analyses that examined treatment-resistant depression and MDD populations with acute suicidal ideation. By integrating findings across partially overlapping meta-analyses, this review clarifies not only whether esketamine is effective, but also when, for whom, and to what extent its effects are clinically meaningful.

Interpretation of antidepressant efficacy and temporal profile

Taken together, the included meta-analyses suggest that the antidepressant effects of intranasal esketamine are largely time-sensitive, with clinical benefits concentrated in the early phase following administration. Although a favorable direction of effect is consistently observed across outcome measures, the extent and durability of symptom

improvement vary across meta-analyses, with differences attributable to assessment timing, patient populations, and analytic approaches (8-10).

Rather than clearly indicating sustained antidepressant efficacy across the full acute treatment period, the overall evidence points to a pattern in which initial symptom reductions diminish over time, particularly in analyses incorporating later acute follow-up assessments (8, 10, 22, 24). This temporal attenuation suggests that the observed benefits may be driven primarily by early pharmacodynamic effects, rather than by cumulative or maintenance-related mechanisms.

Subgroup findings further indicate that larger early effects are not uniformly observed across populations, but appear more prominent in selected contexts, such as treatment-resistant depression or very early assessment windows (10). The observation of more pronounced early effects in TRD warrants cautious interpretation. Clinically, individuals with TRD may present with greater baseline severity and longer illness duration, potentially allowing for larger absolute symptom reductions during rapid-acting interventions. From a mechanistic perspective, it has been proposed that glutamatergic mechanisms may be particularly relevant in TRD, potentially rendering this subgroup more responsive to NMDA-modulating agents in the acute phase (33). Methodologically, greater baseline severity increases the measurable change on continuous scales, regression-to-the-mean effects cannot be excluded, and enriched or selective trial designs may amplify early treatment–placebo contrasts. These factors may collectively contribute to the observed subgroup pattern and should be considered when interpreting early efficacy signals in TRD populations. A similar caution applies to findings derived from very early assessment windows. Acute psychoactive effects, expectancy-related influences, and transient state changes immediately following administration may contribute to larger apparent treatment effects within the first hours (34). Such early signals may not necessarily predict sustained clinical benefit over subsequent follow-up periods.

Evidence regarding administration patterns and dosing remains limited, and available analyses do not support a consistent dose–response relationship, underscoring the need for cautious interpretation of subgroup and dose-related findings (24). In this context, dose- and time-stratified analyses reported by Nikolin et al. demonstrated that both low and high doses were associated with comparable and statistically significant symptom reductions following single-dose administration, whereas repeated dosing and later follow-up assessments were not associated with sustained antidepressant effects (24). Similarly, dose-specific subgroup analyses reported by Oraee et al. suggested that higher fixed or flexible dosing strategies may be associated with more robust early efficacy estimates. However, these findings were not supported by dose–response meta-regression analyses and were accompanied by variable heterogeneity (11). Collectively, these findings indicate that esketamine efficacy is more likely related to early pharmacodynamic effects and the achievement of an adequate, individually tolerated dose rather than reflecting a linear or cumulative dose–response relationship.

From a clinical perspective, the temporal pattern observed across meta-analyses—characterized by rapid onset of effect followed by attenuation over subsequent weeks—has important implications for treatment positioning. Rather than supporting intranasal esketamine as a definitive maintenance strategy, this pattern is more consistent with a short-term “bridge” intervention aimed at rapid symptom stabilization during periods of acute severity or crisis. In this framework, esketamine may serve to accelerate early improvement while longer-term pharmacological or psychosocial treatments take effect. Such positioning aligns more closely with the available evidence than conceptualizing esketamine as a sustained antidepressant maintenance therapy.

Beyond temporal dynamics, the magnitude of observed effects also warrants careful clinical interpretation. A key issue in interpreting these findings is the distinction between statistical and clinical significance. Across meta-analyses reporting absolute changes, adjunctive intranasal esketamine was associated with mean MADRS differences of approximately 1.5 to 4 points compared with place-

bo. Although statistically significant in several analyses, the relationship of these differences to the Minimal Clinically Important Difference (MCID) remains uncertain. MCID estimates for the MADRS vary across methodological approaches, and no universally accepted threshold exists. Differences in the range observed here are likely to represent modest effects at the group level and may not necessarily translate into a clearly perceptible or clinically substantial advantage for the average patient. This distinction is particularly relevant when positioning esketamine within treatment algorithms, where considerations of cost, tolerability, and comparative effectiveness influence clinical decision-making.

Response and remission: temporal patterns and clinical interpretation

Taken together, the available meta-analytic evidence suggests that intranasal esketamine is associated with higher response and remission rates compared with placebo during the acute phase of treatment, with benefits most consistently observed at very early assessment time points (9,10,12).

Only a limited number of meta-analyses examined response and remission across multiple acute time points. In these analyses, later assessments yielded smaller effect estimates compared with very early post-administration outcomes, suggesting a tendency toward attenuation over time (10,12,18). This temporal pattern parallels findings reported for continuous symptom severity measures and supports the interpretation that response and remission outcomes may be particularly sensitive to the timing of assessment, with early benefits not consistently maintained at later acute and follow-up evaluations.

Across meta-analyses, response and remission effect estimates were generally modest in magnitude, although considerable variability was observed across studies. Meta-analyses reporting pooled estimates using relative risks or odds ratios typically indicated favorable but non-uniform effects, with differences attributable to outcome definitions, assessment schedules, background antidepressant treatments, and analytic strategies (6,11,13,18). Where reported, heterogeneity for response and remission outcomes was frequently moderate to high, underscoring the methodological diversity of the included evidence (19,28).

From a clinical perspective, these findings suggest that intranasal esketamine may facilitate early categorical treatment responses, including response and remission, in a subset of patients during the acute phase of treatment. However, the durability of these categorical outcomes across subsequent acute follow-up assessments appears less consistent. Accordingly, response and remission outcomes should be interpreted with careful attention to the timing of assessment and in relation to continuous symptom measures, rather than being viewed as standalone indicators of sustained antidepressant efficacy.

Suicidality and suicidal ideation: interpretation and clinical implications

Evidence on suicidality and suicidal ideation remains more limited and methodologically heterogeneous than the evidence on depressive symptom severity. Across the included meta-analyses, suicidality was assessed using different definitions and instruments, including any available suicidality measure, resolution of suicidality, treatment-period suicidal ideation, and suicide scale scores derived from instruments such as SSI, BSS, BDI, and MSSI (8,10,22,27,28).

Within this heterogeneous evidence base, statistically significant findings were observed mainly at very early assessment time points. Wang et al. (2021) found that, in patients with major depression and suicidal ideation, resolution of suicidality was greater with esketamine than with placebo at 2–4 hours, but not at 24 hours or day 28 (10). Bahji et al. also reported significant reductions in suicidality in the acute phase and at 1 week, whereas the effect at 2 weeks was no longer statistically significant; in their subgroup analysis, the pooled suicidality effect for esketamine remained significant (28). Similarly, Chen et al. (2023) reported significant reductions in suicidal ideation scores for intranasal esketamine at 4–6 hours and 24 hours, while also noting heterogeneity related to diffe-

rences in the included populations and scales (22). In contrast, more recent esketamine-focused syntheses did not support a sustained or overall anti-suicidal effect. Fountoulakis et al. (2025) reported that the effect size concerning suicidality was not significant at any time point and concluded that esketamine showed virtually no beneficial effect over placebo on suicidality (8). Likewise, Wang et al. (2025) found no significant difference between esketamine and placebo in treatment-period suicidal ideation overall, and this outcome remained non-significant across subgroups defined by baseline suicidal ideation status (27).

Taken together, these findings suggest that studies with significant results differed systematically from others primarily in timing of assessment and outcome definition, and to some extent in population. Significant effects were generally confined to the first hours or first week after administration, whereas later assessments were usually non-significant. In addition, some meta-analyses focused specifically on patients with major depression and suicidal ideation, whereas others pooled broader MDD/TRD samples with or without suicidal ideation. Overall, the available meta-analytic evidence supports, at most, a possible early and short-lived reduction in suicidal ideation in some acute-phase analyses, but does not support firm conclusions regarding a sustained anti-suicidal effect of intranasal esketamine.

Relapse prevention and maintenance: limited and heterogeneous evidence

Compared with acute efficacy outcomes, evidence regarding relapse prevention and maintenance effects of intranasal esketamine is derived from a small subset of meta-analyses and remains methodologically heterogeneous. Across the included syntheses, relapse-related outcomes were assessed using differing definitions and statistical approaches, including hazard ratios and risk ratios, with follow-up durations and patient subgroups varying substantially (8,13,15,27).

Within these limitations, available meta-analytic findings generally indicate a directional advantage favoring esketamine in reducing relapse risk during continuation or maintenance treatment. Reduced relapse risk was reported in analyses using hazard ratios among remitter and responder subgroups (13), as well as in analyses reporting hazard ratios or risk ratios for relapse outcomes during continuation or maintenance treatment (15,27). Fountoulakis et al. also discussed relapse and maintenance outcomes based on continuation-phase trials, but were unable to generate pooled relapse estimates due to heterogeneous definitions and the limited number of available maintenance studies (8). However, these findings primarily reflect repeated analyses of data from a small number of randomized withdrawal maintenance trials, most notably SUSTAIN-1. As such, they do not represent independent pooled evidence derived from multiple maintenance-phase randomized trials.

From a clinical perspective, these findings suggest a possible role for intranasal esketamine in short-term relapse prevention during continuation treatment among patients who have achieved response or remission. However, the reliance on a small number of randomized withdrawal trials and the absence of robust, pooled long-term maintenance data preclude firm conclusions regarding sustained relapse prevention. Consequently, current evidence supports cautious interpretation of maintenance effects and highlights the need for longer-term, methodologically consistent studies specifically designed to evaluate relapse prevention efficacy.

Safety and tolerability: Adverse event profiles and treatment discontinuation

Across the included meta-analyses, safety outcomes were most commonly reported in aggregated forms, such as overall adverse event rates, treatment discontinuation, or tolerability indices, rather than as individual symptom categories. Across these syntheses, intranasal esketamine was consistently associated with a higher overall frequency of adverse events compared with placebo, supporting a general signal of increased treatment-related side effects (28,31).

Only three meta-analyses provided detailed, symp-

tom-level adverse event data. Across these analyses, a convergent pattern of non-serious adverse events emerged. The most frequently and consistently reported adverse events were dissociation, dizziness/vertigo, sedative effects, and gastrointestinal symptoms. These adverse events were significantly more common in the esketamine group across all three meta-analyses, despite differences in study populations and analytic approaches. In contrast, headache was not significantly increased and blood pressure–related adverse events were inconsistently reported and did not show a uniform increase across studies (18, 27, 30).

Evidence regarding serious adverse events remains limited and inconclusive. Across the small number of meta-analyses that provided pooled estimates, including analyses reporting risk differences or risk ratios, no statistically significant increase in SAE risk was observed with intranasal esketamine compared with placebo (14, 31). However, interpretation of these findings is constrained by low event rates, short follow-up durations, and reliance on a limited number of contributing trials. As a result, the current meta-analytic evidence does not allow firm conclusions regarding rare or longer-term serious safety outcomes.

Treatment discontinuation outcomes highlight an important distinction between overall treatment acceptability and tolerability driven by adverse events. Across meta-analyses, all-cause discontinuation rates did not differ significantly between intranasal esketamine and placebo, suggesting comparable overall acceptability (24, 32). In contrast, meta-analyses specifically examining discontinuation due to adverse events generally reported higher dropout rates in esketamine-treated groups, including a statistically significant increase in two analyses and a marginally significant increase in another (27, 31, 32), with directionally higher but non-significant estimates also reported elsewhere (28). This pattern suggests that discontinuation may be more closely related to specific non-serious adverse effects, particularly dissociative symptoms, somnolence, and vestibular–perceptual adverse effects, rather than to global treatment acceptability.

From a risk–benefit perspective, the magnitude of symptomatic improvement should be interpreted alongside the substantially elevated risk ratios observed for certain adverse events, particularly vertigo and dissociation. While remission rates show statistically significant advantages over placebo in some analyses, these benefits appear modest in absolute terms. In contrast, relative risks for dissociation and vertigo were markedly increased, implying that the Number Needed to Harm (NNH) for certain non-serious adverse events may approach or even fall below the conceptual Number Needed to Treat (NNT) for remission in some contexts. Although formal NNT and NNH calculations were beyond the scope of this umbrella synthesis, this imbalance underscores the importance of individualized risk–benefit assessment and shared decision-making.

This pattern, together with the finding of similar all-cause discontinuation but higher adverse event–related dropout, points to symptom-specific tolerability concerns rather than reduced overall acceptability. To facilitate clearer interpretation and cross-study comparability, future meta-analyses would benefit from more standardized, symptom-level adverse event reporting.

Interpretation of the umbrella findings should be informed by the methodological quality of the included meta-analyses. Although most included reviews were rated as low or critically low confidence on AMSTAR-2, the two high-quality meta-analyses did not materially contradict the overall direction of the findings. Rather, they supported the evidence for short-term antidepressant efficacy of intranasal esketamine, while providing less consistent or less favorable support for suicidality-related outcomes and tolerability/acceptability. This pattern suggests that the overall conclusions are not solely driven by low-quality evidence; however, confidence should differ across outcome domains, with the strongest support seen for short-term depressive symptom reduction.

The overall certainty of evidence varied across outcomes. While evidence for short-term depressive symptom reduction and non-serious adverse events was relatively more robust, the certainty for suici-

dality-related outcomes and relapse prevention was limited due to heterogeneity across studies and imprecision of available estimates. These findings highlight that, although intranasal esketamine demonstrates consistent short-term antidepressant effects, the strength of evidence supporting other clinically relevant outcomes remains more uncertain.

Clinical implications and contribution of this umbrella review

This umbrella review clarifies the clinical role of intranasal esketamine by emphasizing the timing and durability of its antidepressant effects across meta-analyses. Clinically, this pattern supports positioning esketamine as an adjunctive option for rapid symptom stabilization rather than sustained maintenance treatment. Tolerability concerns, particularly dissociative and vestibular symptoms, should be weighed against modest efficacy gains. By integrating efficacy, temporal profiles, and safety outcomes at an umbrella level, this review delineates the strengths and limits of the current evidence base and underscores the need for standardized outcome reporting and longer-term data in future research.

Limitations

Several limitations should be acknowledged. The calculated CCA indicated a high degree of overlap among the included meta-analyses, reflecting substantial reliance on a limited set of pivotal esketamine randomized controlled trials, many of which were industry-sponsored. This overlap suggests that the apparent breadth of the meta-analytic literature largely represents repeated syntheses of a shared evidence base rather than fully independent bodies of evidence, and therefore the consistency observed across meta-analyses should be interpreted with caution. The literature search was restricted to PubMed/MEDLINE and Scopus databases. Although these databases cover a large proportion of psychiatric research, the exclusion of Embase and the Cochrane Library may have limited retrieval of additional eligible meta-analyses. Methodological heterogeneity across meta-analyses, including differences in patient populations, dosing regimens, outcome definitions, and follow-up durations, and, in some cases, pooling of intranasal and intravenous ketamine administration routes, further constrains direct comparability. A further methodological limitation is the potential for functional unblinding. The acute psychoactive effects of intranasal esketamine, particularly dissociation and vertigo, may have enabled participants and investigators to infer treatment allocation despite formal blinding. This could have influenced subjective outcome reporting and potentially inflated efficacy estimates. Evidence for longer-term efficacy, relapse prevention, and sustained safety remains limited, as most meta-analyses focus on acute treatment phases with relatively short follow-up. Finally, the predominance of industry-sponsored primary trials warrants cautious interpretation, as potential funding-related influences cannot be fully excluded.

This umbrella review synthesizes the available meta-analytic evidence on intranasal esketamine in major depressive disorder and indicates that intranasal esketamine is associated with a rapid-onset antidepressant effect of modest magnitude, with the most pronounced benefits observed in the early post-administration period. Overall, the evidence supports the use of intranasal esketamine as an adjunctive treatment option rather than a standalone or first-line antidepressant, particularly for carefully selected patients in whom rapid symptom reduction is clinically prioritized, rather than for sustained symptom control.

Meta-analytic findings suggest that intranasal esketamine may be associated with transient reductions in suicidal ideation during the very early post-administration period; however, evidence for sustained anti-suicidal, relapse-preventive, or maintenance effects remains limited and methodologically heterogeneous. From a safety perspective, esketamine is consistently associated with increased rates of non-serious adverse events, while serious adverse events and all-cause discontinuation do not appear to be consistently elevated relative to placebo.

Future research should focus on longer-term, independently funded randomized studies with stan-

dardized outcome definitions, clearly specified maintenance endpoints, and comprehensive safety reporting to establish a more precise, evidence-informed clinical positioning of intranasal esketamine across depressive disorders.

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REFERENCES

1. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, Boland E, Weber RP, Randolph C, Bann C. Defining treatment-resistant depression. Depress Anxiety 2020; 37:134-145. doi: 10.1002/da.22968.

2. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, Gorwood P, Ho R, Kasper S, Kennedy SH. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry 2023; 22:394-412. doi: 10.1002/wps.21120.

3. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163:1905-1917. doi: 10.1176/ajp.2006.163.11.1905.

4. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. Exp Clin Psychopharmacol 2015; 23:1-21. doi: 10.1037/a0038550.

5. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, Lane R, Lim P, Duca AR, Hough D. 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; 76:893-903. doi: 10.1001/jamapsychiatry.2019.1189.

6. Papakostas GI, Salloum NC, Hock RS, Jha MK, Murrough JW, Mathew SJ, Iosifescu DV, Fava M. Efficacy of esketamine augmentation in major depressive disorder: a meta-analysis. J Clin Psychiatry 2020; 81:19r12889. doi: 10.4088/JCP.19r12889.

7. Bahji A, Zarate CA, Vazquez GH. Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. Expert Opin Drug Saf 2022; 21:853-866. doi: 10.1080/14740338.2022.2047928.

8. Fountoulakis KN, Saitis A, Schatzberg AF. Esketamine treatment for depression in adults: a PRISMA systematic review and meta-analysis. Am J Psychiatry 2025; 182:259-275. doi: 10.1176/appi.ajp.20240515.

9. Hock RS, Feeney A, Iovieno N, Murrough JW, Mathew SJ, Iosifescu DV, Fava M, Jha MK, Papakostas GI. Rapidity of symptom improvement with intranasal esketamine for major depressive disorder: a systematic review and meta-analysis. J Clin Psychiatry 2022; 84:44591. doi: 10.4088/JCP.21r14086.

10. Wang SM, Kim NY, Na HR, Lim HK, Woo YS, Pae CU, Bahk WM. Rapid onset of intranasal esketamine in patients with treatment-resistant depression and major depression with suicidal ideation: a meta-analysis. Clin Psychopharmacol Neurosci 2021; 19:341-354. doi: 10.9758/cpn.2021.19.2.341.

11. Oraee S, Alinejadfard M, Golsorkh H, Sadeghian M, Fanaei M, Centis R, D'Ambrosio L, Sotgiu G, Goudarzi H, Migliori GB. Intranasal esketamine for patients with major depressive disorder: a systematic review and meta-analysis. J Psychiatr Res 2024; 180:371-379. doi: 10.1016/j.jpsychires.2024.11.010.

12. Calder CN, Kwan AT, Teopiz KM, Wong S, Rosenblat JD, Mansur RB, Rhee TG, Ho R, Cao B, McIntyre RS. Number needed to treat for ketamine and esketamine in adults with treatment-resistant depression: a systematic review and meta-analysis. J Affect Disord 2024; 356:753-762. doi: 10.1016/j.jad.2024.04.039.

13. Jawad MY, Di Vincenzo JD, Ceban F, Jaberi S, Lui LM, Gillissie ES, Alnafeesi Y, Rosenblat JD, McIntyre RS. The efficacy and safety of adjunctive intranasal esketamine treatment in major depressive disorder: a systematic review and meta-analysis. Expert Opin Drug Saf 2022; 21:841-852. doi: 10.1080/14740338.2022.2058488.

14. Floriano I, Silvinato A, Bernardo WM. The use of esketamine in the treatment of patients with oral antidepressant-resistant depression: systematic review and meta-analysis. Rev Assoc Med Bras 2023; 69:e2023D696. doi: 10.1590/1806-9282.2023D696.

15. Naudet F, Pellen C, Fodor LA, Gastaldon C, Barbui C, Turner EH, Le Pabic E, Cristea IA. Efficacy and safety of esketamine for treatment-resistant depression: registered report for a systematic review with an individual patient data meta-analysis of randomized, double-blind, placebo-controlled trials. BMC Med 2025;23(1):677. doi: 10.1186/s12916-025-04435-x.

16. Huang C, Hu L, Liu W, Geng F, Wong GTC, Zhang Y, Reif A, Bao Y, Xue Q, Lu L. Efficacy and safety of esketamine on major depression, postpartum depression and perioperative depression: a systematic review and meta-analysis. Mol Psychiatry 2026; 31:545-558. doi: 10.1038/s41380-025-03320-6.

17. 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; 35:890-900. doi: 10.1177/02698811211013579.

18. Liu P, Zhang SS, Liang Y, Gao ZJ, Gao W, Dong BH. Efficacy and safety of esketamine combined with antidepres-

sants for treatment-resistant depression: a meta-analysis. Neuropsychiatr Dis Treat 2022; 18:2855-2865. doi: 10.2147/NDT.S388764.

19. Gowthami B, Mehta I, Baiju S, Appani A, Suvarna T, Randhawa KS, Kakkad AM, Syed AB, Kumar V, Ramteke HD. Efficacy and safety of esketamine nasal spray in treatment-resistant depression: a systematic review and meta-analysis of randomized controlled trials. medRxiv [Preprint]. 2025. doi: 10.1101/2025.09.22.25336317.

20. Wang L, Chen X, Gu X, De Smedt H, Popova V, Fu DJ, Canuso CM, Drevets WC, Chen G. A meta-analysis of the antidepressant responses in pivotal trials on esketamine nasal spray and atypical antipsychotics. Neuropsychiatr Dis Treat 2023; 19:2857-2870. doi: 10.2147/NDT.S417027.

21. Dold M, Bartova L, Kasper S. Treatment response of add-on esketamine nasal spray in resistant major depression in relation to add-on second-generation antipsychotic treatment. Int J Neuropsychopharmacol 2020; 23:440-445. doi: 10.1093/ijnp/pyaa034.

22. Chen CC, Zhou N, Hu N, Feng JG, Wang XB. Acute effects of intravenous sub-anesthetic doses of ketamine and intranasal inhaled esketamine on suicidal ideation: a systematic review and meta-analysis. Neuropsychiatr Dis Treat 2023; 19:587-599. doi: 10.2147/NDT.S401032.

23. Hieronymus F, López E, Sjögren HW, Lundberg J. Control group outcomes in trials of psilocybin, SSRIs, or esketamine for depression: a meta-analysis. JAMA Netw Open 2025; 8:e2524119. doi: 10.1001/jamanetworkopen.2025.24119.

24. Nikolin S, Rodgers A, Schwaab A, Bahji A, Zarate C, Vazquez G, Loo C. Ketamine for the treatment of major depression: a systematic review and meta-analysis. EClinicalMedicine 2023; 62:102127. doi: 10.1016/j.eclinm.2023.102127.

25. Ouyang Y, Li J. Efficacy of esketamine nasal spray for treatment-resistant depression: a meta-analysis of randomized controlled studies. Medicine (Baltimore) 2025; 104:e41495. doi: 10.1097/MD.0000000000041495.

26. Seshadri A, Prokop LJ, Singh B. Efficacy of intravenous ketamine and intranasal esketamine with dose escalation for major depression: a systematic review and meta-analysis. J Affect Disord 2024; 356:379-384. doi: 10.1016/j.jad.2024.03.137.

27. Wang Z, Jiang L, Ma W, Li X, Gao Q, Lian S, Yu W. Esketamine nasal spray in major depressive disorder: a meta-analysis of randomized controlled trials. Clin Pharmacol Ther 2025; 117:1637-1649. doi: 10.1002/cpt.3555.

28. Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord 2021; 278:542-555. doi: 10.1016/j.jad.2020.09.071.

29. Guo Q, Guo L, Wang Y, Shang S. Efficacy and safety of eight enhanced therapies for treatment-resistant depression: a systematic review and network meta-analysis of randomized controlled trials. Psychiatry Res 2024; 339:116018. doi: 10.1016/j.psychres.2024.116018.

30. Yang S, Wang J, Li X, Wang T, Xu Z, Xu X, Zhou X, Chen G. Adverse effects of esketamine for the treatment of major depressive disorder: findings from randomized controlled trials. Psychiatr Q 2022; 93:81-95. doi: 10.1007/s11126-020-09871-x.

31. Guo H, Tang L, He M, Tang W, Liu J, Wu S, Yuan S, Wang J, Tang X. Comparative safety and tolerability of ketamine and esketamine for major depressive disorder: a systematic review and meta-analysis. Front Pharmacol 2025; 16:1681060. doi: 10.3389/fphar.2025.1681060.

32. Terao I, Tsuge T, Endo K, Kodama W. Comparative efficacy, tolerability and acceptability of intravenous racemic ketamine with intranasal esketamine, aripiprazole and lithium as augmentative treatments for treatment-resistant unipolar depression: a systematic review and network meta-analysis. J Affect Disord 2024; 346:49-56. doi: 10.1016/j.jad.2023.11.023.

33. Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006; 63:856-864. doi: 10.1001/archpsyc.63.8.856.

34. Kryst J, Kawalec P, Mitoraj AM, Pilc A, Lasoń W, Brzostek T. Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials. Pharmacol Rep 2020; 72:543-562. doi: 10.1007/s43440-020-00097-z.

35. Wang YT, Wang XL, Lei L, Guo ZY, Kan FF, Hu D, Gai C, Zhang Y. A systematic review and meta-analysis of the efficacy of ketamine and esketamine on suicidal ideation in treatment-resistant depression. Eur J Clin Pharmacol 2024; 80:287-296. doi: 10.1007/s00228-023-03605-1.

36. Li J, Ma L, Sun H, Li M, Cao Y, Peng Y, Xu J. Efficacy of racemic ketamine or esketamine monotherapy for reducing suicidal ideation in uni- or bipolar depression: a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci 2025; 275:1359-1371. doi: 10.1007/s00406-024-01920-x.