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Review Article

Comparative Efficacy of Esketamine Versus Standard Antidepressants for Rapid Reduction of Suicidal Ideation in Treatment-Resistant Depression: A Meta-Analysis

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ABSTRACT

Background: Acute suicidal ideation in treatment-resistant depression (TRD) requires timely intervention, but rapid improvement in depressive symptoms does not necessarily establish a suicide-specific treatment benefit. Objective: To systematically review and quantitatively synthesize the effects of adjunctive intranasal esketamine versus standard antidepressant-based care on early and short-term suicidal ideation in adults with TRD. Methods: PubMed, Embase, Cochrane CENTRAL, Scopus, and Web of Science were searched for publications from January 2010 through mid-2026, supplemented by trial registries and gray literature. Eligible designs comprised randomized controlled trials and prospective comparative cohorts. Risk of bias was assessed using RoB 2 and the Newcastle–Ottawa Scale. Standardized mean differences (SMDs) were pooled using DerSimonian–Laird random-effects models; heterogeneity was assessed using I^2. Results: Ten studies, comprising eight randomized trials and two prospective cohorts, were reported to include 1,642 participants: 838 receiving adjunctive esketamine and 804 receiving comparator care. Reported effects favored esketamine at 24 hours (SMD −0.58; 95% CI −0.74 to −0.42; I^2=58.4%), 48 hours (SMD −0.52; 95% CI −0.67 to −0.37), and day 28 (SMD −0.34; 95% CI −0.48 to −0.20; all p<0.001). However, unresolved study identities, TRD eligibility, outcome classification, and missing study-level data prevented independent verification. Conclusion: The reported estimates suggest an early benefit for suicidal ideation, but methodological and source-verification concerns preclude a firm TRD-specific efficacy conclusion. These findings do not establish prevention of suicidal behavior or mortality. Verification and reproducible reanalysis are required before clinical recommendations can be supported. Keywords: Esketamine; Depressive Disorder, Treatment-Resistant; Suicidal Ideation; Antidepressive Agents; Systematic Review; Meta-Analysis.

INTRODUCTION

Treatment-resistant depression (TRD) presents a substantial clinical challenge when persistent depressive symptoms coexist with acute suicidal ideation. In this setting, treatment must address both the underlying depressive disorder and the immediate need for comprehensive suicide-risk assessment and management. Although definitions vary across studies, TRD generally involves an inadequate response to at least two antidepressant trials delivered at an adequate dose and duration. Establishing treatment resistance is therefore essential when evaluating interventions intended for this population, because evidence from broader major depressive disorder (MDD) cohorts may not directly answer questions concerning patients with documented treatment failure (1).

The limitations of conventional antidepressant treatment have encouraged investigation of interventions targeting glutamatergic pathways. Esketamine, the S-enantiomer of ketamine and an N-methyl-D-aspartate receptor antagonist, offers a pharmacologically distinct approach to treating depressive symptoms. Its potential for rapid antidepressant effects provides a rationale for evaluating its contribution during periods of acute clinical deterioration (2). However, improvement in overall depression severity, reduction in suicidal ideation, and prevention of suicidal behavior represent distinct outcomes. Evidence supporting one cannot automatically establish the others, and the clinical interpretation of esketamine research depends on maintaining these distinctions (3).

Previous systematic reviews and meta-analyses have evaluated the efficacy and safety of adjunctive intranasal esketamine in MDD, providing an important foundation for understanding its therapeutic role (4,5). Nevertheless, broad estimates of antidepressant efficacy do not necessarily establish the magnitude or timing of an effect on suicidal ideation in patients with confirmed TRD. A suicide-specific synthesis must distinguish total depression scores from individual suicidal-ideation items and dedicated suicidality instruments. It must also account for differences in baseline suicide risk, treatment history, and concurrent care. Where both groups receive hospitalization, clinical monitoring, and newly initiated or optimized antidepressants, the relevant comparison concerns the additional benefit of esketamine within that treatment setting, rather than its efficacy as a replacement for standard care (3).

The temporal interpretation of treatment effects is equally important. An early change in suicidal ideation may have a different clinical significance from improvement observed after several weeks of repeated treatment. Similarly, a between-group difference during ongoing administration does not establish that the benefit persists after treatment discontinuation. Existing work on the longer-term efficacy of intranasal esketamine reinforces the need to distinguish acute response, continued treatment effects, and maintenance of benefit when defining review outcomes (6). For the present question, separating assessments within the first 24–48 hours from outcomes through approximately four weeks provides a clinically relevant framework without implying evidence of long-term suicide prevention.

A focused systematic review with meta-analysis is therefore justified to evaluate whether eligible comparative studies support an incremental reduction in suicidal ideation with adjunctive intranasal esketamine in adults with TRD. Its contribution should lie in population verification, suicide-specific outcome selection, and explicit assessment of treatment effects over time, rather than an assumption that a later search necessarily resolves previous uncertainty. Quantitative synthesis is appropriate where studies address sufficiently comparable populations, interventions, and outcomes; differences in study design, measurement, and risk of bias must inform both pooling decisions and the certainty assigned to the findings.

Accordingly, this review aims to determine whether adjunctive intranasal esketamine, compared with standard antidepressant-based care with placebo nasal spray or a comparable control condition, reduces suicidal ideation in adults with documented TRD and suicidal ideation at baseline. The primary objective is to evaluate between-group differences at 24 and 48 hours after the first administration and during short-term treatment through approximately 28 days. Secondary objectives are to assess depressive symptom response and adverse events, while considering how study design, clinical characteristics, and methodological limitations affect interpretation.

MATERIAL AND METHODS

This systematic review and meta-analysis evaluated the comparative effects of adjunctive intranasal esketamine and standard antidepressant-based care on suicidal ideation in adults with treatment-resistant depression (TRD). The review was organized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. The research question followed the population, intervention, comparator, and outcome structure, focusing on adults with TRD and acute suicidal ideation, adjunctive intranasal esketamine, a standard-care comparator, and changes in suicidal ideation during early and short-term treatment.

Eligible studies were randomized controlled trials or prospective comparative cohort studies involving adults aged 18 years or older with TRD and suicidal ideation at baseline. Treatment resistance was defined as an inadequate response to at least two adequate antidepressant trials. The intervention comprised intranasal esketamine administered alongside oral antidepressant treatment. Eligible comparators included oral antidepressant-based standard care with placebo nasal spray or a comparable standard-care control condition. Studies were required to report quantitative suicidal-ideation outcomes suitable for calculating a between-group effect estimate. Studies without a comparator group, nonhuman investigations, studies evaluating intravenous racemic ketamine rather than intranasal esketamine, and studies without an explicit suicidal-ideation assessment were excluded. Studies were also excluded when the numerical information required for synthesis remained insufficient following attempts to contact the authors.

PubMed, Embase, the Cochrane Central Register of Controlled Trials, Scopus, and Web of Science were searched for publications from January 2010 through mid-2026. Supplementary searches covered ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, psychiatric conference proceedings, and dissertations. The search combined terms describing esketamine, depressive disorders, suicidality, and comparator treatment using the Boolean expression: (“esketamine” OR “intranasal esketamine”) AND (“treatment-resistant depression” OR “TRD” OR “major depressive disorder”) AND (“suicidal ideation” OR “suicidality” OR “suicide risk”) AND (“antidepressants” OR “oral antidepressants” OR “standard of care”).

Retrieved records were deduplicated before title and abstract screening. Potentially eligible reports underwent full-text assessment against the predefined eligibility criteria. Full-text exclusions considered population and intervention eligibility, comparator suitability, availability of quantitative outcomes, and overlap between study populations. Reports describing overlapping cohorts were assessed to avoid including the same participants more than once within a pooled analysis.

Two reviewers independently extracted data using a standardized, pretested collection form. Disagreements were resolved through discussion or consultation with a third reviewer. Extracted study characteristics included author, publication year, country, study design, sample size, participant age and sex distribution, prior treatment history, and baseline suicidal-ideation severity. Intervention data included esketamine dose, administration frequency, concurrent antidepressant treatment, comparator characteristics, and follow-up duration. Numerical outcome data were extracted for each treatment group at the relevant assessment times.

The primary outcome was the between-group difference in suicidal-ideation change at 24 and 48 hours after the first administration and during short-term follow-up through 28 days. Eligible measures included the suicidal-ideation item of the Montgomery–Åsberg Depression Rating Scale, the Scale for Suicide Ideation, and relevant components of the Columbia–Suicide Severity Rating Scale. Suicidal-ideation outcomes were distinguished from overall depressive symptom severity. Secondary outcomes comprised depressive symptom response, remission, and adverse events.

Risk of bias in randomized trials was assessed using the Cochrane Risk of Bias 2 tool. Assessment addressed the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. Prospective cohort studies were evaluated using the Newcastle–Ottawa Scale, covering participant selection, comparability of study groups, and outcome assessment.

Statistical analyses were conducted using R version 4.3.1 with the meta and metafor packages, supplemented by Review Manager version 5.4. Continuous suicidal-ideation outcomes were summarized using standardized mean differences with 95% confidence intervals to accommodate differences in measurement scales. Negative effect

estimates indicated greater reductions in suicidal ideation with adjunctive esketamine. Dichotomous response and remission outcomes were expressed as risk ratios with 95% confidence intervals. Random-effects pooling used the DerSimonian–Laird estimator to account for anticipated between-study variability.

Statistical heterogeneity was evaluated using the I^2 statistic and interpreted alongside differences in populations, interventions, outcome instruments, and study designs. Subgroup analyses examined study design and esketamine dosing regimen. Leave-one-out sensitivity analyses assessed the influence of individual studies on the pooled estimates. Potential small-study effects were examined visually using funnel plots and statistically using Egger's regression and Begg's rank correlation tests. These assessments were interpreted as investigations of funnel-plot asymmetry rather than definitive tests for the presence or absence of publication bias.

RESULTS

The searches identified 1,248 records from databases and registries and 32 additional records from gray literature, yielding 1,280 records overall. After removal of 412 duplicates, 868 records underwent title and abstract screening, of which 812 were excluded. Full-text assessment was undertaken for 56 reports, and 46 were excluded, leaving ten studies for synthesis (Table 1). Reported reasons for full-text exclusion included overlapping cohorts, unsuitable comparators, and insufficient numerical outcome data; counts for individual reasons were not provided.

The ten listed studies comprised eight randomized controlled trials and two prospective observational cohorts published between 2018 and 2026. Their reported sample sizes summed to 1,642 participants, including 838 receiving adjunctive intranasal esketamine and 804 receiving comparator treatment (Table 2). Individual study samples ranged from 68 to 226 participants. Across studies, reported mean ages ranged from 38.4 to 48.2 years, and female representation ranged from 58.5% to 64.2% (Table 3). The randomized studies were described as comparing esketamine plus standard care with placebo nasal spray plus standard care, whereas the observational studies used standard oral antidepressant care as the comparator. Reported suicidal-ideation measures included the MADRS suicidal-ideation item, SSI, and C-SSRS.

Table 1. Study identification and selection

Selection stage	Number
Records identified through databases and registries	1,248
Additional records identified through gray literature	32
Total records identified	1,280
Duplicate records removed	412
Records screened by title and abstract	868
Records excluded during initial screening	812
Full-text reports assessed for eligibility	56
Full-text reports excluded	46
Studies included in the synthesis	10
Randomized controlled trials	8
Prospective observational cohort studies	2

The manuscript does not provide separate counts for individual full-text exclusion reasons or distinguish database yields from registry yields.

Table 2. Reported characteristics of included studies

Study as listed	Design	Esketamine/control, n	Total, n	Esketamine intervention	Comparator	Reported suicidal-ideation measure
Canuso et al. (2018)	RCT	33/35	68	84 mg twice weekly plus SOC	Placebo nasal spray plus SOC	MADRS suicidal-ideation item
Fu et al. (2020)	RCT	114/112	226	84 mg twice weekly plus SOC	Placebo nasal spray plus SOC	MADRS suicidal-ideation item
Ionescu et al. (2021)	RCT	115/111	226	84 mg twice weekly plus SOC	Placebo nasal spray plus SOC	MADRS suicidal-ideation item
Takahashi et al. (2021)	RCT	102/100	202	56/84 mg twice weekly plus SOC	Placebo nasal spray plus SOC	MADRS suicidal-ideation item
Sussman et al. (2022)	Prospective cohort	68/62	130	Adjunctive esketamine plus optimized oral antidepressants	Standard oral antidepressant care	C-SSRS
Popova et al. (2023)	RCT	112/109	221	Flexible-dose 56/84 mg plus SOC	Placebo nasal spray plus SOC	MADRS suicidal-ideation item; SSI

Study as listed	Design	Esketamine/control, n	Total, n	Esketamine intervention	Comparator	Reported suicidal-ideation measure
McIntyre et al. (2024)	RCT	89/87	176	84 mg twice weekly plus SOC	Placebo nasal spray plus SOC	MADRS suicidal-ideation item
Zhao et al. (2024)	RCT	76/74	150	56/84 mg twice weekly plus SOC	Placebo nasal spray plus SOC	SSI
Gomez et al. (2025)	Prospective cohort	54/52	106	Adjunctive esketamine plus optimized oral antidepressants	Standard oral antidepressant care	C-SSRS
Alvarez et al. (2026)	RCT	75/62	137	Flexible-dose 56/84 mg plus SOC	Placebo nasal spray plus SOC	MADRS suicidal-ideation item
Total	8 RCTs; 2 cohorts	838/804	1,642	—	—	—

RCT, randomized controlled trial; SOC, standard of care; MADRS, Montgomery–Åsberg Depression Rating Scale; SSI, Scale for Suicide Ideation; C-SSRS, Columbia–Suicide Severity Rating Scale.

Entries reproduce the submitted manuscript rather than corrected primary-study records. Study identities, analysis populations, dosing details, and outcome labels require reconciliation before publication. A listed instrument does not establish which score was extracted or that it was a primary efficacy endpoint.

Table 3. Reported population characteristics and methodological appraisal

Characteristic	Reported finding
Publication period	2018–2026
Individual study sample size	68–226
Study mean ages	38.4–48.2 years
Female representation across studies	58.5%–64.2%
Stated population	Adults with TRD and acute suicidal ideation
RCT appraisal tool	Cochrane RoB 2
RCTs described as low risk	6
RCTs described as "moderate risk"	2
Reported concerns in RCTs	Deviations from intended interventions and handling of missing outcome data
Cohort appraisal tool	Newcastle–Ottawa Scale
Cohorts described as high quality	2
Study-specific appraisal judgments and supporting reasons	NR
Newcastle–Ottawa item scores and totals	NR
Outcome-specific GRADE assessments	NR

TRD, treatment-resistant depression. "Moderate risk" reproduces the manuscript's wording; it is not a standard RoB 2 category and cannot be relabeled without the underlying assessments. TRD eligibility remains to be verified study by study.

Table 4. Reported pooled effects on suicidal ideation by assessment time

Assessment time	Contributing studies, n	Analyzed participants, n	Effect size, SMD	95% CI	I^2, %	Effect p-value	Heterogeneity p-value
24 hours after first dose	NR	NR	−0.58	−0.74 to −0.42	58.4	<0.001	0.010
48 hours after first dose	NR	NR	−0.52	−0.67 to −0.37	NR	<0.001	NR
Day 28	NR	NR	−0.34	−0.48 to −0.20	NR	<0.001	NR

SMD, standardized mean difference; CI, confidence interval. Negative estimates favor adjunctive esketamine. The total review sample of 1,642 cannot be assumed to contribute to every analysis. The supplied manuscript does not identify the statistic underlying the reported heterogeneity p-value.

Table 5. Reported subgroup effects on suicidal ideation at 24 hours

Study-design subgroup	Studies in review, n	Studies contributing to subgroup estimate, n	Effect size, SMD	95% CI	I^2, %	Effect p-value	Between-subgroup interaction p-value
Randomized controlled trials	8	NR	−0.55	−0.69 to −0.41	34.1	<0.001	NR
Prospective observational cohorts	2	NR	−0.66	−0.92 to −0.40	64.8	<0.001	NR

The number of studies in each design category is not necessarily the number contributing to the 24-hour analysis. No statistical comparison between subgroup effects was supplied.

Table 6. Reported sensitivity analyses and assessments of small-study effects

Analysis	Reported result	Estimate	95% CI	p-value	Reporting limitation
Leave-one-out analysis	No individual study was described as disproportionately influential	NR	NR	NR	Omission-specific estimates and heterogeneity statistics absent
Dosing-regimen subgroup analysis	Flexible dosing was described as producing a slightly greater reduction	NR	NR	NR	Subgroup estimates, study counts, and interaction test absent
Funnel-plot inspection	Distribution described as largely symmetrical	Not applicable	Not applicable	Not applicable	Plot and contributing study count unavailable
Egger's regression	No statistically significant asymmetry reported	Intercept −0.84	−2.15 to 0.47	0.188	Analyzed outcome/timepoint and model details not specified
Begg's rank correlation	No statistically significant asymmetry reported	NR	NR	0.242	Correlation statistic and analyzed study count absent

Table 7. Reporting status of prespecified secondary outcomes

Secondary outcome	Quantitative findings	Effect estimate and 95% CI	I^2	p-value
Overall depressive symptom response	NR	NR	NR	NR
Remission	NR	NR	NR	NR
Adverse events	NR	NR	NR	NR

The manuscript's methodological appraisal classified six randomized trials as having low risk of bias and two as having "moderate risk," with concerns relating to deviations from intended interventions or missing outcome data. The two cohort studies were described as high quality following Newcastle–Ottawa assessment (Table 3). Study-specific judgments, supporting explanations, and numerical cohort appraisal scores were not supplied; consequently, these aggregate descriptions do not establish outcome-specific risk of bias or certainty of evidence.

At 24 hours after the first dose, the reported pooled effect favored adjunctive esketamine, with an SMD of −0.58 (95% CI −0.74 to −0.42; p<0.001). Heterogeneity at this assessment was I^2=58.4%, with a reported heterogeneity p-value of 0.010. The reported effect at 48 hours was −0.52 (95% CI −0.67 to −0.37; p<0.001), and the day-28 estimate was −0.34 (95% CI −0.48 to −0.20; p<0.001) (Table 4). Heterogeneity estimates and analysis-specific participant counts were not supplied for the latter assessments. Although the later estimate was numerically closer to zero, no formal comparison of effects across timepoints was reported.

In the reported 24-hour subgroup analysis, randomized trials yielded an SMD of −0.55 (95% CI −0.69 to −0.41; p<0.001; I^2=34.1%), while prospective cohorts yielded an SMD of −0.66 (95% CI −0.92 to −0.40; p<0.001; I^2=64.8%) (Table 5). The absence of an interaction test prevents concluding that treatment effects differed by study design. Flexible dosing was described as producing a slightly greater reduction than fixed dosing, but numerical subgroup results were not supplied.

Leave-one-out analyses were reported to show no disproportionate influence from an individual study, although omission-specific estimates were unavailable (Table 6). Funnel-plot inspection was described as showing approximate symmetry. Egger's regression produced an intercept of −0.84 (95% CI −2.15 to 0.47; p=0.188), and Begg's test yielded p=0.242. These results did not identify statistically significant asymmetry but do not exclude publication bias or other small-study effects. Quantitative findings for depressive response, remission, and adverse events were not reported (Table 7). No assessable figures accompanied the supplied results.

DISCUSSION

This review examined whether adjunctive intranasal esketamine reduces suicidal ideation more rapidly than standard antidepressant-based care in adults with treatment-resistant depression (TRD). The reported pooled estimates favored esketamine at 24 hours, 48 hours, and day 28, with a smaller numerical effect at the later assessment. However, unresolved questions concerning study eligibility, outcome extraction, and analysis-specific denominators limit confidence in these findings. The synthesis therefore suggests a possible incremental benefit during acute treatment but does not establish a reliable TRD-specific anti-suicidal effect. Moreover, differences between the pooled estimates across timepoints should not be interpreted as evidence of diminishing efficacy without accounting for the studies and participants contributing to each analysis.

The direction of the reported effects is broadly compatible with previous reviews supporting the antidepressant efficacy of adjunctive intranasal esketamine (4,5). Nevertheless, agreement in the direction of benefit does not establish agreement in the outcome being measured. Overall depressive symptom severity incorporates several domains beyond suicidal thinking, and improvement in a total depression score cannot be treated as equivalent to improvement in suicidal ideation. This distinction is central to interpreting the literature on ketamine and esketamine, in which depressive symptoms, suicidal thoughts, and suicidal behavior have been evaluated using different instruments and study designs (3). The present review's intended contribution is its focus on suicide-specific outcomes at clinically relevant early assessments; that contribution remains dependent on confirming that each pooled estimate was derived from the appropriate outcome rather than a broader depression measure.

Population differences further complicate comparisons with existing evidence. Studies enrolling patients with MDD and acute suicidal ideation do not necessarily establish treatment resistance, while studies enrolling patients with TRD may differ in the severity and immediacy of baseline suicide risk. Applying findings across these populations requires explicit consideration of treatment history, baseline symptom burden, and the clinical circumstances of enrollment. Expert evaluations of ketamine and esketamine emphasize the importance of patient selection and treatment context when interpreting efficacy and implementation evidence (1). Accordingly, a TRD-specific conclusion requires documentation that the analyzed participants met the review's treatment-resistance criteria. If that requirement cannot be established, the review question and its population claims must be reconsidered rather than assuming that all included depressive disorders represent the same clinical group.

The comparator also determines the meaning of the observed treatment effect. Because esketamine was administered alongside antidepressant-based care, the reported estimates concern its additional contribution within a treatment package. Differences in concurrent medications, inpatient management, monitoring, and supportive care could influence improvement in both groups and alter the apparent incremental benefit. The numerically smaller estimate at day 28 might reflect several factors, including changes in either treatment group, differences in contributing studies, or selective availability of follow-up data. It cannot be attributed specifically to conventional antidepressants "catching up." Similarly, improvement during repeated administration does not establish persistence after treatment cessation, a distinction relevant to the interpretation of longer-term esketamine evidence (6).

Heterogeneity at 24 hours indicates that the studies may not estimate a single clinically uniform treatment effect. Plausible sources include differences in baseline suicidal-ideation severity, treatment resistance, outcome instruments, dosing schedules, and the intensity of concurrent care. These factors matter clinically because a similar standardized effect may represent different absolute changes across scales and populations. Standardization permits numerical comparison across instruments but does not ensure that they measure equivalent constructs or have comparable sensitivity to change. Interpretation would therefore benefit from instrument-specific analyses and, where defensible, translation into changes on a familiar scale. The present SMDs alone are insufficient to determine whether the observed differences crossed a clinically meaningful threshold (6,7).

The lower reported heterogeneity among randomized trials than among observational cohorts is compatible with differences in design and clinical variability, but it does not identify their cause. The somewhat larger observational estimate could reflect a treatment association, residual confounding, or differences in patient selection and care delivery. With only two cohorts listed in the review, explanations of their heterogeneity are particularly uncertain. Furthermore, no interaction test was supplied to establish that effects differed by study design. The reported dosing comparison is similarly inconclusive because subgroup estimates and formal comparisons were unavailable. These findings support presenting randomized and observational evidence separately and treating dosing-related observations as exploratory (8,9).

Several limitations directly affect the credibility and reproducibility of this synthesis. Complete citations and source records were not established for all listed studies, and discrepancies in study characteristics require reconciliation. Study-level effect estimates, variance data, and outcome-specific participant counts were unavailable, preventing independent reproduction of the pooled results. The reporting also does not establish how different scale components, missing observations, multiple reports, and assessment windows were handled. Although the manuscript describes risk-of-bias assessment, aggregate quality labels without study-specific justifications

cannot substantiate low risk of bias across the pooled outcomes. The absence of outcome-specific certainty assessments further limits the strength of any clinical recommendation (10,11)

The reporting-bias and sensitivity analyses provide limited reassurance. Nonsignificant Egger and Begg tests cannot exclude selective publication or selective outcome reporting, particularly when the number of studies contributing to each analysis is unclear. Likewise, a statement that leave-one-out analyses were stable does not demonstrate robustness without the corresponding estimates. Incomplete reporting of adverse events, response, and remission also prevents a balanced assessment of benefit and harm. These omissions are consequential because rapid symptom improvement must be interpreted alongside treatment tolerability and the broader requirements of acute clinical care (12,13)

Clinically, the reported findings justify further examination of adjunctive esketamine as part of comprehensive treatment, but they do not support replacing suicide-risk assessment or established acute-care measures. Nor do they establish reductions in suicide attempts, mortality, or hospitalization duration. Pharmacological plausibility arising from glutamatergic mechanisms provides a rationale for investigation, but it cannot demonstrate that an effect on suicidal ideation is independent of improvement in depression (2,3). Policy recommendations should therefore depend on verified suicide-specific outcomes, transparent certainty assessment, and adequately reported safety findings.

The immediate research priority is to audit the included reports, confirm population eligibility, and reproduce each timepoint-specific analysis from traceable extraction data. Future trials should distinguish confirmed TRD from broader MDD populations, prespecify a validated suicidal-ideation endpoint, standardize early assessment times, and document concurrent care. Studies should report suicidal behavior and adverse events separately from symptom scores and extend follow-up beyond the acute dosing period (14, 15).Larger, appropriately designed investigations are also needed to evaluate whether early changes in suicidal ideation predict sustained clinical benefit and whether treatment effects differ according to baseline risk, prior treatment failure, or care setting (16).

CONCLUSION

The reported synthesis suggests that adjunctive intranasal esketamine may provide an early reduction in suicidal ideation compared with standard antidepressant-based care, but unresolved study eligibility, outcome identification, and reproducibility concerns prevent a firm conclusion for adults with TRD. The findings do not establish prevention of suicidal behavior or mortality and are insufficient to support changes in practice independently of comprehensive clinical assessment. Verification of the evidence base, and reproducible, suicide-specific analyses are essential before the magnitude, clinical relevance, and certainty of the proposed benefit can be determined.

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