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Research article

Rapid effects of ketamine and esketamine on suicidal ideation in acute psychiatric settings: A systematic review and meta-analysis

Running title: Ketamine and rapid reduction in suicidal ideation

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Abstract: *Background:* Suicide represents a major global health challenge requiring rapidly acting interventions. Ketamine and intranasal esketamine have demonstrated rapid antidepressant effects, but the extent to which their effects on suicidal ideation are distinct from mood improvement remains uncertain. We conducted a systematic review and meta-analysis to evaluate the efficacy and safety of ketamine/esketamine for suicide-specific outcomes in acute clinical settings. *Methods:* Following PRISMA 2020 guidelines, we searched major databases through June 29, 2025. Randomized

controlled trials and eligible controlled feasibility studies evaluating ketamine or esketamine in patients with suicidal ideation were included. The primary quantitative synthesis evaluated suicide-specific outcomes within 24 h of treatment. Random-effects models using restricted maximum likelihood estimation with Hartung–Knapp adjustment were used to calculate pooled Hedges' *g*. We conducted sensitivity and exploratory subgroup analyses and assessed the certainty of evidence using GRADE. *Results:* Fifteen studies (N = 1509) met the inclusion criteria, of which seven independent controlled studies (N = 567) contributed to the primary ≤24-h quantitative synthesis. The pooled effect was $g = -1.24$ (95% CI: −2.87 to 0.39; $I^2 = 93.3\%$), indicating substantial heterogeneity and considerable imprecision. The estimate was strongly influenced by Pathak et al.; exclusion of this study yielded a more moderate effect ($g = -0.59$; 95% CI: −1.00 to −0.19; $I^2 = 71.6\%$). Exploratory subgroup analyses showed no statistically significant differences by route of administration, clinical setting, or diagnosis. No statistically significant difference in serious adverse events was detected (RR = 1.22; 95% CI: 0.60–2.49; $I^2 = 0\%$), although the confidence interval was wide. Evidence concerning whether reductions in suicidal ideation were partly dissociable from improvements in depressive symptoms was indirect and exploratory. *Conclusions:* Ketamine and esketamine may produce rapid reductions in suicidal ideation in some acute clinical settings; however, the magnitude of benefit remains uncertain because of substantial heterogeneity, imprecision, and sensitivity to an influential study. Evidence regarding the relationship between improvements in suicidal ideation and depressive symptoms remains exploratory. These findings support cautious interpretation of short-term symptomatic benefit and highlight the need for larger, methodologically rigorous trials to clarify durability, safety, and population-specific effects.

Keywords: ketamine; esketamine; depression; major depressive disorder; suicide

1. Introduction

Suicide remains a major global public health concern, accounting for more than 700,000 deaths annually and ranking among the leading causes of death worldwide, particularly among adolescents and young adults [1,2]. Beyond mortality, suicidal crises are associated with substantial psychological suffering, functional impairment, and healthcare utilization. The acute and often fluctuating nature of suicidal states, characterized by intense psychological pain, hopelessness, and impaired cognitive flexibility, creates an urgent need for interventions capable of producing rapid symptom relief [3]. Although conventional antidepressants and psychotherapeutic interventions are effective for long-term risk reduction, their delayed onset of action leaves a critical therapeutic gap during acute suicidal episodes [4,5].

The identification of ketamine's rapid antidepressant properties has substantially altered the landscape of biological psychiatry. Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, and its S-enantiomer, esketamine, exert effects that differ mechanistically from traditional monoaminergic antidepressants [6]. Preclinical and clinical studies suggest that NMDA receptor blockade initiates downstream modulation of glutamatergic transmission, increases brain-derived neurotrophic factor (BDNF), activates mammalian target of rapamycin (mTOR) signaling, and enhances synaptic plasticity within corticolimbic circuits implicated in mood regulation [7]. These

mechanisms are thought to underlie the rapid onset of antidepressant effects observed within hours of administration, contrasting sharply with the delayed effects of conventional agents [7,8].

Beyond antidepressant action, accumulating evidence suggests that ketamine and esketamine may produce rapid reductions in suicidal ideation [9,10]. Randomized controlled trials in major depressive disorder and bipolar depression have reported decreases in suicide-specific measures within 24 h of administration [11,12]. Notably, some studies have observed temporal dissociation between improvements in suicidal ideation and overall depressive symptom reduction, raising the possibility that suicidal ideation effects may not be entirely mediated by mood improvement alone [13]. Proposed mechanisms include rapid attenuation of psychological pain, reductions in hopelessness, modulation of inflammatory pathways, and alterations in cognitive rigidity associated with suicidal states [14]. However, the extent to which these effects reflect distinct neurobiological pathways versus accelerated antidepressant response remains incompletely understood.

Previous systematic reviews and meta-analyses have examined ketamine's effects on depressive symptoms and, in some cases, suicidal ideation [15,16]. However, focused syntheses evaluating suicide-specific outcomes across different routes of administration (intravenous versus intranasal), acute clinical settings (e.g., emergency departments versus inpatient units), and diagnostic subgroups remain limited. Moreover, important questions persist regarding the magnitude and durability of early suicidal ideation effects, the influence of dosing strategies, safety profiles in acutely suicidal populations, and the degree to which observed benefits may be partially independent of antidepressant mechanisms [17]. Clarifying these dimensions is essential to inform clinical decision-making, guideline development, and regulatory evaluation in emergency psychiatric care.

Accordingly, the present systematic review and meta-analysis aims to comprehensively evaluate the efficacy and safety of ketamine and esketamine for suicide-specific outcomes in acute settings. We specifically examine (i) the magnitude and temporal profile of suicidal ideation effects, (ii) exploratory evidence regarding dissociation from antidepressant response, and (iii) potential moderating factors including route of administration, clinical setting, and diagnostic characteristics. By synthesizing available randomized evidence, this study seeks to provide a balanced and clinically relevant assessment of the role of ketamine-based interventions in acute suicide prevention.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [18]. We conducted a literature search across multiple electronic databases, including PubMed, Scopus, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and Web of Science, from database inception through June 29, 2025. The search strategy has included a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to ketamine interventions and suicide outcomes. The search strategy included the following key terms and keywords: [ketamine OR esketamine OR "S-ketamine" OR "2-(2-chlorophenyl)-2-(methylamino)cyclohexanone" OR "ketamine hydrochloride"] AND (suicide* OR "suicidal ideation" OR "suicidal thoughts" OR "self-harm" OR "suicide attempt" OR "suicide risk" OR "suicide

prevention" OR "suicidal behavior") AND ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "placebo" OR "randomly" OR "trial" OR RCT).

Additional searches were performed in clinical trial registries, conference abstracts, and the reference lists of included and relevant studies to identify any missing eligible studies that were not captured by the primary search strategy.

2.2. Eligibility criteria

Studies were included if they met the following criteria: randomized controlled trial (RCT) design, or any other feasibility assessment studies that aimed to compare ketamine or esketamine to placebo, active control, or standard care; adult or adolescent participants (≥13 years) with documented suicidal ideation, suicide attempts, or elevated suicide risk; primary or secondary outcome measures specifically assessing suicide-related parameters including validated suicidal ideation scales and suicide attempt rates; and availability of sufficient statistical data for meta-analysis. Studies were excluded if they focused only on substance use disorders without concurrent mood disorders; enrolled participants without baseline suicidal ideation or elevated suicide risk; did not investigate acute settings or assess safety and efficacy; or lacked extractable data on suicide-specific outcomes despite author contact attempts.

2.3. Study selection and data extraction

Extracted data included study design variables, sample sizes, participant age and gender distributions, psychiatric diagnoses, baseline suicide severity scores, intervention protocols including drug formulation, dosage, route of administration, and frequency, control group characteristics, outcome measures and assessment timepoints, adverse events and safety parameters, and statistical results including means, standard deviations, effect sizes, and confidence intervals (CI).

2.4. Eligibility for the primary quantitative synthesis

Studies included in the systematic review were further assessed for eligibility for the primary quantitative synthesis of early suicidal ideation outcomes. Quantitative pooling was restricted to independent controlled studies reporting a suicide-specific outcome within 24 h of the first relevant ketamine or esketamine administration and providing sufficient comparative data to derive a harmonized standardized effect estimate. Studies were retained in the qualitative synthesis but excluded from the primary meta-analysis when the relevant assessment occurred after repeated treatment, when no concurrent control group was available, when continuous comparative data were insufficient for calculation of the standardized effect estimate, or when the report represented a secondary or pooled analysis of an already included trial population. Supplementary Table S1 details study-level eligibility and the analytic handling of all 15 included reports.

2.5. Risk of bias assessment

We assessed risk of bias across key methodological domains, including random sequence generation, allocation concealment, participant blinding, outcome-assessor blinding, incomplete

outcome data, selective reporting, and other potential sources of bias. We categorized domain-level judgments as low risk, some concerns, or high risk, and assigned an overall risk-of-bias judgment to each study. For secondary, pooled, or nonrandomized reports, we designated domains not applicable to the study design as not applicable (N/A). Supplementary Table S2 presents detailed study-level assessments.

2.6. Statistical analysis

We conducted meta-analyses using random-effects models with restricted maximum likelihood (REML) estimation and Hartung–Knapp adjustment. Effect sizes were expressed as Hedges' *g* for continuous outcomes and risk ratios (RRs) for dichotomous outcomes, with 95% confidence intervals (CIs). We assessed statistical heterogeneity using the I^2 statistic, τ^2, and Cochran's Q test, and calculated a 95% prediction interval for the primary outcome. Sensitivity analyses examined the influence of the Pathak et al [26]. study and selected study-level and analytical characteristics, including risk of bias, industry funding, sample size, and model specification. Subgroup analyses according to route of administration, clinical setting, and psychiatric diagnosis were considered exploratory because of the small number of contributing studies. We explored small-study effects and potential publication bias using Egger's regression test and Begg's rank correlation test, with cautious interpretation because fewer than 10 studies contributed to the primary quantitative synthesis.

3. Results

3.1. Study selection and characteristics

The literature search identified 198 records from electronic databases, with no additional records identified from other sources. After removing 80 duplicate records and 19 records identified as ineligible by automated tools, 99 records underwent title and abstract screening. After excluding 51 irrelevant records, 48 reports were retrieved and assessed for eligibility. Following full-text assessment, 15 studies met the inclusion criteria and were included in our study, with varying numbers included in specific meta-analyses depending on the availability of outcomes (Figure 1).

The 15 included studies encompassed 1509 participants (Table 1). Fourteen studies were randomized controlled trials, and one was a single-arm feasibility study, with sample sizes ranging from 10 to 451 participants. Participant ages ranged from 13 to 80 years; only one study specifically enrolled adolescents (Zhou et al. 2024) [20], whereas the remaining studies involved adults. Study populations were clinically heterogeneous, including major depressive disorder (MDD) as well as mixed diagnostic populations comprising bipolar disorder, post-traumatic stress disorder, anxiety disorders, adjustment disorders, and other mood disorders. Clinical settings included emergency departments, inpatient units, outpatient services, and mixed settings. Intervention protocols also varied substantially. Ketamine was administered predominantly by the intravenous route at doses of 0.2–0.5 mg/kg, while esketamine was administered intranasally, generally at a fixed dose of 84 mg; one study evaluated oral ketamine at 3 mg/kg. Comparators included saline or matching placebo preparations and active-control midazolam. Suicide-specific outcomes were assessed using several instruments, including the MSSI, SSI, C-SSRS, CGI-SS-r, MADRS-SI, and BSI/BSS, with assessment time points ranging from minutes after administration to longer-term follow-up. This clinical and methodological diversity was considered when interpreting the quantitative synthesis.

Furthermore, of the 15 included reports summarized in Table 1, seven independent controlled studies provided sufficiently comparable and extractable data for inclusion in the primary ≤24-h quantitative synthesis; study-specific inclusion and exclusion decisions are provided in Supplementary Table S1.

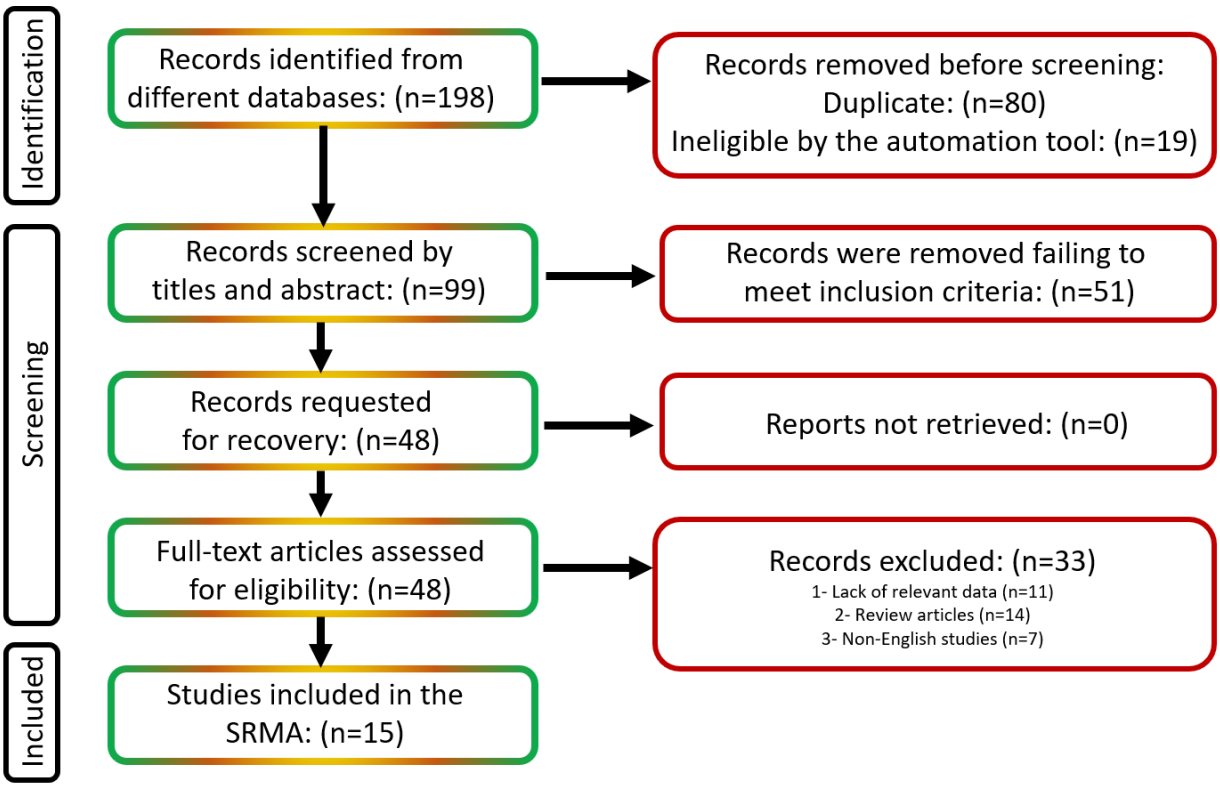


Figure 1. PRISMA flow diagram depicting the identification, screening, eligibility assessment, and inclusion of studies for the systematic review and meta-analysis of the effects of ketamine and esketamine on suicidal ideation. A total of 15 studies were included in the final analysis, identified from electronic databases, and no additional records were identified from other sources.

Table 1. Characteristics, demographics, interventions, and suicide-specific outcome assessments of included studies.

Study	Design	Setting/country	N	Mean age	Primary diagnosis population	Intervention	Control	Suicide-specific outcome/relevant timepoint	Follow-up
Seraj et al. 2025 [19]	RCT	Outpatient/inpatient; country NR	80	NR	MDD	Oral ket, 3 mg/kg, single dose	Oral midazolam, 0.3 mg/kg	MSSI; 4 h after dose; also days 3 and 7	7 days
Zhou et al. 2024 [20]	RCT	Inpatient; China	54	NR	MDD	IV Esket 0.25 mg/kg, 3 infusions	IV midazolam, 0.02 mg/kg	C-SSRS; 24 h after final infusion (day 6)	4 weeks
Hochschild et al. 2022 [21] †	RCT	Inpatient; USA	80 †	Same as Grunebaum 2018†	MDD	IV ket, 0.5 mg/kg	IV midazolam, 0.02 mg/kg	SSI; 24 h after infusion	Secondary analysis of day-1 outcome
Gaither et al. 2022 [22]	Single-arm study	Emergency department; USA	14	NR	Mixed psychiatric diagnoses	IV ket, 0.5 mg/kg, single dose	None	C-SSRS; 2 h; also 6 h	6 h
Abbar et al. 2022 [23]	Double-blind RCT	Inpatient; France	156	Median 40‡	Bipolar, depressive disorders	IV ket, 0.5 mg/kg	IV saline placebo	SSI; assessments from 40 min to 72 h; primary trial endpoint = full SI remission at day 3	6 weeks
Ionescu et al. 2021 [24]	Phase 3 RCT—ASPIRE II	Inpatient; multinational	227	40.8 ± 13.1	MDD	Intranasal Esket, 84 mg	Matching intranasal placebo	CGI-SS-r; 24 h after first dose	90 days
Domany 2022 [25]	Double-blind-RCT	Emergency department; USA	30	35.4 ± 9.0§	Transdiagnostic acute SI	Intranasal ket, 40 mg, single dose	Intranasal saline placebo	BSS and MADRS-SI; 4 h after dose	28 days
Pathak et al. 2021 [26]	Single-blind study	Inpatient; India	60	31.7¶	Depressive disorders	IV ket, 0.5 mg/kg	IV saline placebo	MSSI; 6 h after first infusion, then daily	1 week
Canuso et al. 2021 [27] ‖	ASPIRE I + II	Inpatient; multinational	451‖	40.1 ± 13.0	MDD	Intranasal Esket, 84 mg	Matching intranasal placebo	CGI-SS-r; 4 and 24 h after first dose	90 days
Fu et al. 2020 [28]	Phase 3 RCT ASPIRE I	Inpatient; multinational	224	39.3 ± 12.9	MDD	Intranasal Esket, 84 mg	Matching intranasal placebo	CGI-SS-r; 24 h after first dose	90 days
Domany et al. 2020 [29]	Double-blind RCT	Emergency department; USA	18	NR	Depression with SI	IV ket, 0.2 mg/kg, single dose	IV saline placebo	BSS; 90–240 min after dose	14 days

Continued on next page

Study	Design	Setting/country	N	Mean age	Primary diagnosis population	Intervention	Control	Suicide-specific outcome/relevant timepoint	Follow-up
Grunebaum et al. 2018 [30] †	Double-blind RCT	Inpatient; USA	80	39.6 ± 3.1¶	MDD with SI	IV ket, 0.5 mg/kg, single dose	IV midazolam, 0.02 mg/kg	SSI; 24 h after infusion; also 230 min	6 weeks
Canuso et al. 2018 [31]	Double-blind RCT	Inpatient; multinational	66	NR	MDD	Intranasal Esket, 84 mg	Matching intranasal placebo	MADRS-SI/BSS; acute assessments including 4 and ~24 h	81 days
Burger et al. 2016 [32]	Double-blind RCT	Military emergency department; USA	10	~27¶	Depression	IV ket, 0.2 mg/kg, single dose	IV saline placebo	BSS; serial assessment through 4 h	2 weeks
Murrough et al. 2015 [33]	RCT	Outpatient/inpatient; USA	24	NR	MDD and bipolar depression with SI	IV ket, 0.5 mg/kg, single dose	IV midazolam, 0.045 mg/kg	BSI; 24 h after infusion	7 days

Note: BSI/BSS: Beck Scale for Suicide Ideation; CGI-SS-r: Clinical Global Impression–Severity of Suicidality–Revised; C-SSRS: Columbia-Suicide Severity Rating Scale; ED: emergency department; IV, intravenous; MADRS-SI: Montgomery–Åsberg Depression Rating Scale suicidal-thoughts item; MDD: major depressive disorder; MSSI: Modified Scale for Suicidal Ideation; NR: not reported/ascertainable from the available report; RCT: randomized controlled trial; SI: suicidal ideation; SOC: standard of care; SSI Scale for Suicide Ideation. †: Hochschild et al. (2022) [21] is not an independent trial. It explicitly states that data from the published Grunebaum et al. (2018) [30] RCT were used in its post hoc analysis; both, therefore, represent the same NCT01700829 trial population. Accordingly, Hochschild should remain in the systematic review for its secondary mechanistic/dissociation analysis but must not be treated as an independent study in quantitative pooling. ‡: Abbar reports median age, rather than mean age, in the accessible study report; I would preserve it as “Median 40” rather than manufacture a mean. The study reports 68% women. §: Domany 2022 [25] reports a mean overall age of approximately 35.4 years in our audited extraction, but the sex data available in the study table were incomplete for the full N=30. ¶: Overall values calculated descriptively from the reported equal-sized treatment arms. These are not separately reported overall means in the source. For example, Pathak reports 16 and 18 women in its two groups and arm-specific ages. If we want Table 1 to contain only author-reported overall demographics, I would instead show the two arm-specific values rather than calculated overall values. ‖: Canuso et al. (2021) [27] is a pooled secondary analysis of ASPIRE I and ASPIRE II, not a third independent ASPIRE trial. The authors explicitly state that they pooled efficacy and safety data from the two pivotal studies. ASPIRE I and II have separate registrations, NCT03039192 and NCT03097133. Thus, Canuso 2021 should not be pooled simultaneously with Fu 2020 and Ionescu 2021 for the same outcome.

3.2. Suicide-specific outcomes

Standardized mean differences (Hedges' *g*) with 95% confidence intervals (CIs) are shown using a random-effects model with restricted maximum likelihood (REML) estimation and Hartung–Knapp adjustment. The pooled effect at ≤24 h was $g = -1.24$ (95% CI: −2.87 to 0.39), with substantial between-study heterogeneity ($I^2 = 93.3\%$). The 95% prediction interval was −5.67 to 3.20. In sensitivity analysis excluding the influential Pathak et al. (2021) [26] study, the pooled effect was $g = -0.59$ (95% CI: −1.00 to −0.19; $I^2 = 71.6\%$). Negative values indicate greater reduction in suicidal ideation with ketamine/esketamine.

Seven independent studies provided extractable data for the ≤24-h suicide-specific quantitative synthesis (Figure 2). Using a random-effects model with restricted maximum likelihood (REML) estimation and Hartung–Knapp adjustment, the pooled standardized mean difference was $g = -1.24$ (95% CI: −2.87 to 0.39), with substantial heterogeneity ($\tau^2 = 2.84$; $I^2 = 93.3\%$). The 95% prediction interval (−5.67 to 3.20) indicated considerable uncertainty in the expected effect across clinical settings. Individual study effect sizes ranged from −0.13 (Ionescu et al., 2021) [24] to −5.32 (Pathak et al., 2021) [26]. Because Pathak et al. [26] represented an extreme and influential estimate, sensitivity analysis excluding this study yielded a more moderate pooled effect of $g = -0.59$ (95% CI: −1.00 to −0.19), although residual heterogeneity remained substantial ($I^2 = 71.6\%$). Thus, the primary pooled estimate was imprecise and highly sensitive to the influential Pathak et al. [26] study, whereas the sensitivity analysis indicated a more moderate short-term reduction in suicidal ideation.

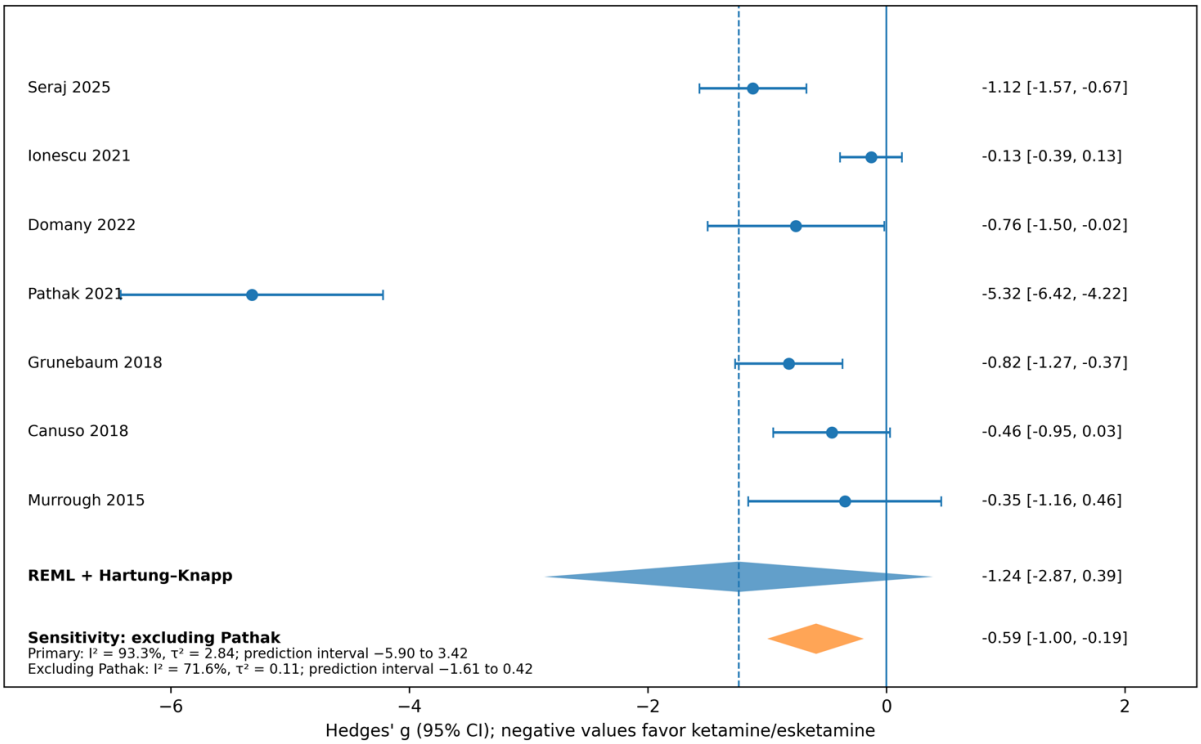


Figure 2. Forest plot of suicide-specific outcomes comparing ketamine/esketamine versus control.

Table 2 summarizes suicide-specific outcome measures, corresponding depression measures, early treatment effects, response or remission outcomes where available, and exploratory evidence regarding the relationship between changes in suicidal ideation and depressive symptoms. Across studies, suicidal ideation was assessed using several validated instruments, including the Modified Scale for Suicidal Ideation (MSSI), Scale for Suicidal Ideation (SSI), Columbia-Suicide Severity Rating Scale (C-SSRS), Clinical Global Impression–Severity of Suicidality–Revised (CGI-SS-r), Montgomery–Åsberg Depression Rating Scale suicide item (MADRS-SI), and Beck Scale for Suicide Ideation (BSI/BSS).

Where standardized effect sizes were estimable, the magnitude of early reduction in suicidal ideation varied considerably across studies. Seraj et al. (2025) [19] and Grunebaum et al. (2018) [30] demonstrated comparatively large early effects, whereas Ionescu et al. (2021) [24] and Murrough et al. (2015) [33] showed smaller or nonsignificant between-group effects. Pathak et al. (2021) [26] reported an exceptionally large effect at 6 h after the first infusion; this estimate was subsequently examined in influence and sensitivity analyses because of its substantial contribution to between-study heterogeneity. Several additional studies reported categorical response or remission outcomes rather than continuous data suitable for standardized effect-size estimation. Secondary and pooled publications with overlapping participant samples were retained for complementary analyses but were not treated as independent datasets in quantitative synthesis.

Exploratory analyses of the relationship between improvement in suicidal ideation and depressive symptoms yielded heterogeneous findings. Some studies reported temporal patterns, mediation analyses, or differences in the relative magnitude of suicidal-ideation and depression outcomes that were compatible with partial dissociation, whereas others showed broadly concordant changes in both domains. Notably, the secondary analysis by Hochschild et al. (2022) [21] found that changes in core mood, depression, and anxiety symptoms explained 51.6% of the variance in SSI reduction, indicating a substantial relationship between improvement in mood symptoms and suicidal ideation. Overall, these findings do not establish that the reduction in suicidal ideation occurs independently of antidepressant effects; rather, they suggest that the relationship may vary across studies and should be regarded as exploratory and hypothesis-generating.

3.3. Descriptive safety profile across included studies

Risk ratios (RRs) with 95% confidence intervals (CIs) are shown on a logarithmic scale using a random-effects model. Across 6 independent studies, 18 serious adverse events occurred among 402 participants receiving ketamine/esketamine compared with 13 events among 406 control participants. The pooled estimate was RR = 1.22 (95% CI: 0.60–2.49; $I^2 = 0\%$), indicating no statistically significant between-group difference. The wide confidence interval reflects the low event rate and limited precision and does not exclude a clinically meaningful increase or decrease in risk.

Safety assessment across six independent studies with extractable serious adverse event data encompassed 808 participants (402 intervention and 406 control) (Table 3, Figure 3). The pooled random-effects meta-analysis showed no statistically significant between-group difference in serious adverse events (RR = 1.22, 95% CI: 0.60–2.49), with no observed heterogeneity ($\chi^2 = 2.83$, df = 5; $I^2 = 0\%$). Serious adverse events occurred in 18/402 participants (4.5%) receiving ketamine/esketamine and 13/406 controls (3.2%). Although no statistically significant increase in risk was detected, the wide confidence interval indicates substantial uncertainty and does not exclude a clinically meaningful

increase in serious adverse events. The most commonly reported non-serious adverse events included dissociation, transient blood pressure elevation, dizziness, nausea, and sedation, although their frequency and reporting varied considerably across studies. These events were generally transient and occurred during the monitored post-administration period. No consistent signal of increased serious adverse events was identified; however, the relatively small number of events and wide confidence intervals limit the precision of the safety estimate.

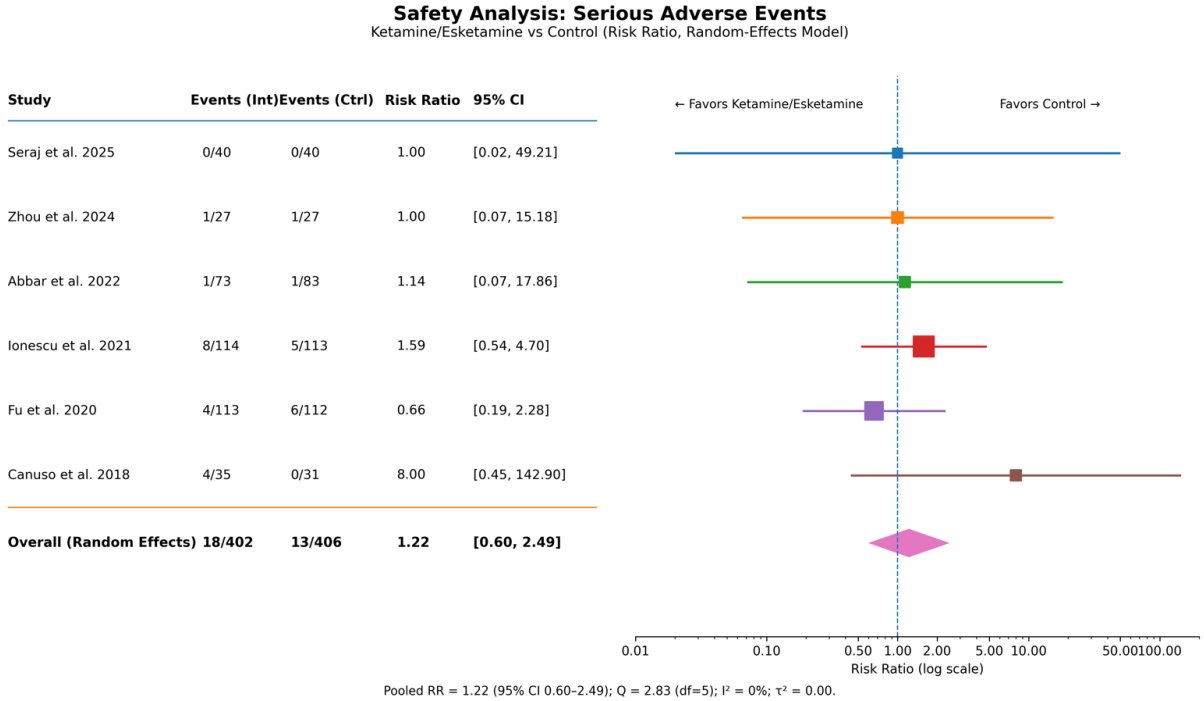


Figure 3. Forest plot of serious adverse events comparing ketamine/esketamine versus control.

Table 2. Suicide-specific outcomes, response measures, and exploratory relationship with depression.

Study	Suicide-specific measure	Suicide effect, *g* (95% CI)	Depression measure	Depression *g* (95% CI)	Suicide response remission	Exploratory relationship with depression AND Acute SI outcome and timepoint
Seraj et al. 2025 [19]	MSSI	−1.12 (−1.57, −0.67)	HAM-D17	−0.92 (−1.36, −0.48)	NR	SI and depression both improved acutely; no specific mediation or temporal dissociation analysis reported Lower SI at 4 h after single oral dose; benefit also reported at days 3 and 7
Zhou et al. 2024 [20]	C-SSRS ideation	NR; change-score/repeated-treatment data	MADRS	NR; change-score data	RR 1.30 (0.82–2.05)	SI and depression both improved following repeated treatment; evidence for independent SI effect not established Repeated-treatment outcome assessed 24 h after third infusion (day 6)
Hochschild et al. 2022† [21]	SSI	Not separately pooled†	HDRS-24/mood-factor measures	Not separately pooled†	—	Mood/depression and anxiety changes explained 51.6% of variance in SSI reduction across treatment groups; analysis supports substantial association rather than mechanistic independence 24 h after infusion; secondary analysis of Grunebaum 2018 trial
Gaither et al. 2022 [22]	C-SSRS Severity	NR; single-arm	IMS mood	NR; single-arm	NR	No controlled assessment of whether SI improvement was independent of mood change Improvement at 2 h, maintained at 6 h; single-arm study
Abbar et al. 2022 [23]	SSI	NR; median/categorical data	IDS-C30	NR; non-comparable reporting format	Full SI remission significantly favored ketamine at day 3	Mediation analysis implicated psychological/mental pain; relationship between SI and general depressive improvement remains exploratory Rapid assessments from 40 min; remission evaluated through 72 h, with primary trial endpoint at day 3
Ionescu et al. 2021 (ASPIRE II) [24]	CGI-SS-r	−0.13 (−0.39, 0.13)	MADRS	−0.35 (−0.61, −0.09)	RR 1.05 (0.74–1.50)	Depression improved more clearly than clinician-rated suicidality; no evidence of an SI-specific effect independent of mood improvement 24 h after first dose; between-group SI difference not significant

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Study	Suicide-specific measure	Suicide effect, *g* (95% CI)	Depression measure	Depression *g* (95% CI)	Suicide response remission	Exploratory relationship with depression AND Acute SI outcome and timepoint
Domany & McCullumsmith 2022 [25]	BSS / MADRS-SI	≈−0.76 (−1.50, −0.02) ‡	MADRS	NR	MADRS-SI remission: 80% vs. 33% at 4 h	SI and depression both improved at 4 h; study does not establish mechanistic independence Reduction in SI at 4 h after single intranasal dose
Pathak et al. 2021 [26]	MSSI	−5.32 (−6.42, −4.22)	HAM-D17	−2.40 (−3.07, −1.73)	NR	SI effect was numerically much larger than depression effect, but this is indirect evidence only and should not be interpreted as proof of an independent mechanism Marked reduction at 6 h after first infusion
Canuso et al. 2021§ [27]	CGI-SS-r	Not independently pooled§	MADRS	Not independently pooled§	RR 1.66 (1.25–2.20) at reported acute response assessment	Pooled secondary analysis of ASPIRE trials; SI and depressive outcomes should not be considered independent evidence from Fu/Ionescu 4 and 24 h after first dose; pooled ASPIRE I + II analysis
Fu et al. 2020 (ASPIRE I) [28]	CGI-SS-r	NR; ranked/LS-type estimate not suitable for primary SMD	MADRS	NR; LS mean difference reported	RR 1.77 (1.09–2.87) for reported response measure	Significant depression improvement accompanied by no significant CGI-SS-r difference; does not support a distinct SI-specific effect 24 h after first dose; between-group difference not statistically significant
Domany et al. 2020 [29]	BSS	NR; insufficient extractable continuous comparative data	MADRS	NR	SI remission at 90 min: 88% vs. 33%	Depression and SI both assessed, but available report does not provide sufficient evidence to establish independence Acute SI reduction evident within 90–180 min after IV ketamine
Grunebaum et al. 2018† [30]	SSI	−0.82 (−1.27, −0.37)	HDRS-17	Depression effect not statistically significant at day 1 in original trial	SSI response: 55% vs. 30% at day 1	Mediation analysis indicated that improvement in depression accounted for part, but not all, of the SI effect; interpretation remains exploratory 24 h after single infusion; primary endpoint
Canuso et al. 2018 [31]	MADRS-SI / BSS	−0.46 (−0.95, 0.03)	MADRS	−0.53 (−1.02, −0.04)	RR 2.19 (0.95–5.04)	SI and depressive effects were of similar magnitude; no clear evidence of dissociation Acute assessment at 4 and ~24 h after first intranasal dose

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Study	Suicide-specific measure	Suicide effect, *g* (95% CI)	Depression measure	Depression *g* (95% CI)	Suicide response remission	Exploratory relationship with depression AND Acute SI outcome and timepoint
Burger et al. 2016 [32]	BSS	NR; very small analyzable sample	BHS	NR	NR	Pilot study was not designed to formally separate SI effects from broader affective/hopelessness changes Serial assessments through 4 h after IV ketamine
Murrough et al. 2015 [33]	BSI	−0.35 (−1.16, 0.46)	MADRS	−0.53 (−1.35, 0.29)	NR	Both estimates were imprecise; no firm evidence that SI reduction was independent of antidepressant improvement 24 h after infusion

Note: NR: not reported or not estimable in a format suitable for standardized effect-size calculation; BHS: Beck Hopelessness Scale; BSS/BSI: Beck Scale for Suicide Ideation; CGI-SS-r: Clinical Global Impression–Severity of Suicidality–Revised; C-SSRS: Columbia–Suicide Severity Rating Scale; HAM-D/HDRS: Hamilton Depression Rating Scale; IDS-C30: Inventory of Depressive Symptomatology–Clinician Rated; MADRS: Montgomery–Åsberg Depression Rating Scale; MADRS-SI: MADRS suicidal-thoughts item; MSSI: Modified Scale for Suicidal Ideation; SSI: Scale for Suicidal Ideation. †: Hochschild et al. (2022) [21] is a post hoc secondary analysis of the Grunebaum et al. (2018) [30] randomized trial and is presented only for complementary analyses of the relationship between mood and suicidal ideation; the overlapping sample was not independently pooled. ‡: Effect size calculated from extractable group-level BSS change data reported in the publication; negative values favor ketamine. §: Canuso et al. (2021) [27] is a post hoc pooled analysis of ASPIRE I (Fu et al., 2020) [28] and ASPIRE II (Ionescu et al., 2021) [24]and was not treated as an independent dataset when the parent trials were included.

Table 3. Safety and adverse events profile.

Study	Safety N	Serious AE, int/ctrl	Dissociation, int	BP elevation	Discontinuation due to AE, int/ctrl	Other notable safety findings
Seraj 2025 [19]	80	0/40 vs. 0/40	17.50%	NR	0/40 vs. 0/40	No serious adverse events reported
Zhou 2024 [20]	54	1/27 vs. 1/27	55.60%	14.80%	2/27 vs. 3/27	Adverse effects monitored following repeated IV esketamine
Hochschild 2022† [21]	80	Not independently assessed†	NR	NR	NR	Secondary safety information belongs to parent Grunebaum trial
Gaither 2022 [22]	14	0/14; no control	NR	NR	1/14; no control	One infusion stopped because of dizziness/dysphoria; single-arm feasibility study
Abbar 2022 [23]	156	1/73 vs. 1/83‡	9.6%§	NR	NR	Reported effects included sedation, depersonalization/derealization, nausea, and dizziness

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Study	Safety N	Serious AE, int/ctrl	Dissociation, int	BP elevation	Discontinuation due to AE, int/ctrl	Other notable safety findings
Ionescu 2021 (ASPIRE II) [24]	227	8/114 vs. 5/113	38.60%	6.10%	NR	Dissociative effects and BP increases generally resolved by ~1.5 h
Domany & McCullumsmith 2022 [25]	30	0/15 vs. 0/15	NR	NR	0/15 vs. 0/15	No serious adverse events; study explicitly underpowered for safety conclusions
Pathak 2021 [26]	60	NR	NR	NR	0/30 vs. 0/30	Detailed comparative AE reporting limited
Canuso 2021¶ [27]	451	Not independently pooled¶	33.90%	11.50%	6.2% vs. 3.6%	Pooled secondary safety analysis of ASPIRE I + II
Fu 2020 (ASPIRE I) [28]	225#	4/113 vs. 6/112	29.20%	16.80%	4.4% vs. 4.5%	Common AEs included dizziness, dissociation, headache, nausea, and somnolence
Domany et al. 2020 [29]	18	0/9 vs. 0/9	NR	22.00%	0/9 vs. 0/9	No serious adverse events reported
Grunebaum 2018 [30]	80	Not suitable for acute comparative SAE pooling	NR	NR	0/40 vs. 0/40	Ten SAEs were reported across study/follow-up periods; no suicide occurred during the protocol
Canuso 2018 [31]	66	4/35 vs. 0/31	31.40%	NR	5/35 vs. 1/31	Dissociation and transient BP elevations generally resolved within ~2 h
Burger 2016 [32]	10	0/5 vs. 0/5	0%	NR	0/5 vs. 0/5	No serious acute safety signal reported in a small pilot
Murrough 2015 [33]	24	NR	NR	NR	0% vs. 0%	Acute adverse effects were monitored; comparative SAE data not sufficiently reported

Note: AE: adverse event; BP: blood pressure; Ctrl: control; Int: intervention; NR: not reported. † Hochschild et al. (2022) [21] is a secondary analysis of the Grunebaum et al. (2018) [30] trial. ‡ SAE denominators correspond to the study safety groups reported for adverse-event assessment. § Reported as depersonalization/derealization. ¶ Canuso et al. (2021) [27] pooled ASPIRE I and II and was therefore not treated as an independent dataset when the parent trials were included. # Safety population used for SAE analysis.

Table 4. Subgroup analyses.

Subgroup type	Subgroup name	Studies (k)	Participants (N)	Suicide effect size, Hedges' *g* (95% CI)	I^2	*P* for subgroup difference
Route	Intravenous (IV)	3	164	−2.14 (−8.92, 4.65)	96.70%	0.608
	Intranasal	3	323	−0.33 (−1.06, 0.39)	40.30%	
	Oral	1	80	−1.12 (−1.57, −0.67)	—	
Age group	Adults (≥18 years)	7	567	−1.24 (−2.87, 0.39)	93.30%	—
	Adolescents (13–17 years)	0	—	Not estimable	—	—
Setting	Emergency department	1	30	−0.76 (−1.50, −0.02)	—	0.865
	Inpatient unit	4	433	−1.64 (−5.48, 2.20)	96.40%	
	Mixed/outpatient	2	104	−0.81 (−5.61, 3.98)	62.30%	
Diagnosis	Major depressive disorder	4	453	−0.61 (−1.31, 0.09)	82.30%	0.323
	Mixed diagnoses	3	114	−2.12 (−8.95, 4.71)	96.50%	

Note: CI: Confidence interval; NR: Not reported; IV: intravenous; I^2: I-squared heterogeneity statistic.

3.4. Publication bias assessment

Assessment of small-study effects and potential publication bias was limited by the small number of studies contributing to the primary quantitative synthesis. Egger's regression test and Begg's rank correlation test were therefore conducted as exploratory analyses and interpreted cautiously. Neither test provided statistically significant evidence of small-study effects; however, the limited number of studies and substantial heterogeneity preclude firm conclusions regarding the presence or absence of publication bias. Supplementary Table S3 presents detailed results.

3.5. Subgroup analyses

Subgroup analyses were conducted on the seven independent studies contributing to the primary ≤24-h quantitative synthesis and were considered exploratory because of the small number of studies within individual categories (Table 4). Numerical differences were observed across routes of administration. Intravenous ketamine showed the largest pooled effect (Hedges' $g = -2.14$; 95% CI: −8.92, 4.65; $I^2 = 96.7\%$), although the estimate was highly imprecise and heterogeneous. Intranasal treatment showed a smaller and more consistent estimate ($g = -0.33$; 95% CI: −1.06, 0.39; $I^2 = 40.3\%$), while oral ketamine was represented by a single study ($g = -1.12$; 95% CI: −1.57, −0.67). The test for subgroup differences by administration route was not statistically significant ($P = 0.608$), providing no evidence that route modified the treatment effect.

Setting-based analyses similarly showed no statistically significant subgroup difference ($P = 0.865$). The emergency department category was represented by a single study ($g = -0.76$; 95% CI: −1.50, −0.02), whereas pooled estimates for inpatient ($g = -1.64$; 95% CI: −5.48, 2.20; $I^2 = 96.4\%$) and mixed/outpatient settings ($g = -0.81$; 95% CI: −5.61, 3.98; $I^2 = 62.3\%$) were imprecise. Diagnostic subgroup analyses also did not demonstrate significant effect modification ($P = 0.323$). Studies restricted to major depressive disorder yielded a pooled effect of $g = -0.61$ (95% CI: −1.31, 0.09; $I^2 = 82.3\%$), compared with $g = -2.12$ (95% CI: −8.95, 4.71; $I^2 = 96.5\%$) in mixed-diagnostic populations. All seven studies included in the primary quantitative synthesis involved adults; therefore, an age-based subgroup comparison was not estimable. Overall, the wide confidence intervals, substantial within-subgroup heterogeneity, and small number of contributing studies preclude conclusions regarding differential efficacy by administration route, clinical setting, or diagnostic category.

3.6. Sensitivity analyses

Sensitivity analyses demonstrated that the magnitude and precision of the pooled estimate were sensitive to the influential Pathak et al. (2021) [26] study (Supplementary Table S4). In the primary analysis of seven independent studies, the pooled effect was Hedges' $g = -1.24$ (95% CI: −2.87 to 0.39), with substantial heterogeneity ($I^2 = 93.3\%$; $\tau^2 = 2.84$). Exclusion of Pathak et al. (2021) [26], which reported an extreme effect estimate ($g = -5.32$), produced a more moderate pooled effect of $g = -0.59$ (95% CI: −1.00 to −0.19) and reduced heterogeneity to $I^2 = 71.6\%$. These findings indicate that this study strongly influenced the magnitude of the primary pooled estimate and the degree of between-study heterogeneity. Accordingly, we placed greater interpretive emphasis on the sensitivity analysis excluding Pathak et al. [26] than on the magnitude of the primary pooled estimate.

3.7. Risk-of-bias assessment

Risk-of-bias assessment indicated variable methodological limitations across the included studies (Supplementary Table S2). Concerns primarily related to randomization and allocation procedures, blinding, incomplete outcome data, and limitations associated with particular study designs. Blinding was a particular challenge because the characteristic psychoactive and dissociative effects of ketamine or esketamine may have increased the likelihood of treatment assignment being recognized. Nevertheless, several randomized trials incorporated active comparators or matching placebo

procedures to reduce this risk. The identified methodological limitations were considered when interpreting the pooled estimates and contributed to the assessment of certainty for the primary suicide-specific outcome.

3.8. GRADE evidence assessment

The certainty of evidence was assessed using the GRADE framework (Supplementary Table S5). For the primary ≤24-h suicide-specific outcome, the certainty of evidence was rated low, principally because of substantial inconsistency across studies and imprecision in the pooled estimate. Considerable heterogeneity, the wide confidence and prediction intervals, and the sensitivity of the pooled estimate to the influential Pathak et al. (2021) [26] study reduced confidence in the precision and generalizability of the estimated magnitude of short-term benefit.

Certainty assessments for secondary efficacy and safety outcomes were likewise interpreted cautiously because of differences in outcome definitions, assessment instruments, treatment protocols, follow-up periods, and the relatively small number of studies contributing to individual analyses. Accordingly, the GRADE assessment supports cautious interpretation of the evidence: ketamine or esketamine may produce rapid symptomatic reduction in suicidal ideation in some acute clinical settings, but the magnitude of this effect remains uncertain and should not be interpreted as evidence of established suicide prevention or comparative superiority of a particular administration route.

4. Discussion

Suicide remains a global public health emergency requiring timely and effective interventions. Despite advances in pharmacological and psychotherapeutic approaches, most established psychiatric treatments require weeks to achieve meaningful therapeutic benefit, leaving patients vulnerable during acute suicidal crises. Inpatient suicide continues to occur despite existing preventive measures, underscoring the limitations of current strategies in high-risk psychiatric settings [34–36]. Interventions that produce rapid symptom relief therefore address a critical unmet clinical need.

Our systematic review and meta-analysis synthesized evidence from over 1500 participants and provided a focused evaluation of suicide-specific outcomes. In the primary ≤24-h quantitative synthesis of seven independent controlled studies (N = 567), the pooled effect was $g = -1.24$ (95% CI: −2.87 to 0.39), with substantial heterogeneity ($I^2 = 93.3\%$) and considerable imprecision. The wide confidence interval and prediction interval (−5.67 to 3.20) indicate substantial uncertainty in both the magnitude and consistency of the effect across clinical settings. Accordingly, the pooled estimate should not be interpreted as a precise or universally applicable treatment effect.

The substantial heterogeneity was strongly influenced by Pathak et al. (2021) [26], which reported an unusually large effect relative to the other included studies. Exclusion of this study reduced the pooled estimate to $g = -0.59$ (95% CI: −1.00 to −0.19) and heterogeneity to $I^2 = 71.6\%$. Although the effect became more moderate, substantial residual heterogeneity remained, indicating that between-study variability could not be attributed to a single study alone. Differences in patient populations, clinical settings, treatment protocols, outcome measures, and study methodology may have contributed to this variability.

Assessment of small-study effects and publication bias was necessarily exploratory because only seven independent studies contributed to the primary quantitative synthesis. Neither Egger's regression (*P*

= 0.074) nor Begg's rank correlation (P = 0.543) provided statistically significant evidence of small-study effects; however, these tests have limited power when fewer than 10 studies are available, particularly with substantial heterogeneity. Publication bias therefore cannot be reliably confirmed or excluded.

Exploratory subgroup analyses showed numerical variation according to route of administration, clinical setting, and diagnostic group, but none of the between-group differences were statistically significant. For route of administration, the pooled estimates were g = −2.14 (95% CI: −8.92 to 4.65) for intravenous administration, g = −0.33 (95% CI: −1.06 to 0.39) for intranasal administration, and g = −1.12 (95% CI: −1.57 to −0.67) for the single oral study, with no significant subgroup difference (P = 0.608). These comparisons were based on small numbers of studies and indirect cross-study contrasts rather than head-to-head comparisons and should therefore be regarded as hypothesis-generating rather than evidence of differential efficacy according to route of administration.

Evidence regarding the relationship between improvement in suicidal ideation and depressive symptoms remains suggestive rather than definitive. Several included studies reported temporal differences between changes in suicidality and mood, while mediation analyses suggested that improvement in mood accounted for only part of the observed change in suicidal ideation. Such findings are compatible with, but do not establish, partially distinct therapeutic mechanisms. Therefore, whether reductions in suicidal ideation reflect distinct neurobiological pathways or an early manifestation of antidepressant response the remains uncertain. Proposed mechanisms for ketamine's rapid clinical effects include modulation of glutamatergic neurotransmission, synaptic plasticity, and downstream neurotrophic signaling pathways [37], but the relationship between these mechanisms and changes in suicidal ideation remains incompletely established.

Previous systematic reviews and expert syntheses have examined ketamine's antidepressant and suicidal-ideation effects across diverse psychiatric populations [38,39]. The present review extends this literature by focusing on suicide-specific outcomes and examining short-term effects across different clinical settings, administration routes, and diagnostic groups. However, these comparisons remain exploratory, and the limited number of contributing studies precludes conclusions regarding comparative efficacy between treatment approaches.

Safety assessment across six independent controlled studies with extractable serious adverse-event data (N = 808) showed no statistically significant difference between ketamine/esketamine and control groups (RR = 1.22; 95% CI: 0.60–2.49; I^2 = 0%). However, the small number of serious adverse events and wide confidence interval limit the precision of this estimate and do not exclude clinically important risks. Dissociative and related symptoms were reported in several studies and were generally transient. Feasibility studies in emergency settings suggest that carefully monitored administration in acute-care environments may be achievable [22]; nevertheless, appropriate clinical monitoring remains important.

Several limitations should be considered. Substantial heterogeneity and imprecision reduce confidence in a single summary effect, while the small number of studies contributing to the primary synthesis limits the statistical power of subgroup and small-study-effect analyses. Evidence in adolescents remains particularly limited, with only one included study addressing this population [40]. Blinding is challenging because the psychoactive effects of ketamine and esketamine may reveal treatment allocation, and the predominance of major depressive disorder samples limits generalizability to other psychiatric diagnoses. Exclusion of individuals with active substance-use disorders in several trials may further limit applicability to typical emergency presentations. Short follow-up periods preclude conclusions regarding prevention of suicide attempts, suicide mortality, or

long-term safety. The certainty of evidence for the primary suicide-specific outcome was therefore rated low.

Overall, the available evidence suggests that ketamine or esketamine may produce rapid symptomatic reduction in suicidal ideation in some acute clinical settings, but the magnitude and consistency of this effect remain uncertain. A short-term reduction in suicidal ideation should not be interpreted as evidence of suicide prevention or as a substitute for comprehensive suicide-risk assessment, monitoring, and ongoing clinical management. Future research should prioritize adequately powered randomized trials using standardized suicide-specific outcome measures and assessment timepoints, direct comparisons of administration approaches where clinically appropriate, longer-term follow-up to assess durability and safety, greater representation of adolescents and other understudied populations, and further investigation of the relationship between changes in mood and suicidal ideation.

5. Conclusions

This systematic review and meta-analysis suggests that ketamine and esketamine may produce rapid reductions in suicidal ideation in some acute psychiatric settings. Across seven independent controlled studies contributing to the primary ≤24-h quantitative synthesis, the pooled estimate was $g = -1.24$ (95% CI: −2.87 to 0.39), with substantial heterogeneity ($I^2 = 93.3\%$) and considerable imprecision. The estimate was strongly influenced by Pathak et al. (2021) [26]; exclusion of this study yielded a more moderate effect ($g = -0.59$; 95% CI: −1.00 to −0.19; $I^2 = 71.6\%$). These findings indicate that the magnitude of the short-term effect is uncertain and varies considerably across studies and clinical contexts.

No statistically significant difference in serious adverse events was detected between ketamine/esketamine and control groups (RR = 1.22; 95% CI: 0.60–2.49; $I^2 = 0\%$). However, the small number of events and wide confidence interval preclude firm conclusions regarding safety. Evidence examining the relationship between reductions in suicidal ideation and improvements in depressive symptoms was indirect and exploratory; therefore, the available data do not establish that changes in suicidal ideation occur independently of changes in depressive symptoms.

Exploratory subgroup analyses showed numerical differences according to route of administration, clinical setting, and diagnostic group, but none of the between-group differences were statistically significant. These analyses were limited by the small number of contributing studies and should not be interpreted as evidence of differential efficacy between intravenous, intranasal, or oral administration. Overall, the certainty of evidence for the primary outcome was low, reflecting substantial inconsistency, imprecision, and methodological limitations. The findings therefore support cautious interpretation of a possible short-term symptomatic benefit rather than a precise or broadly generalizable treatment effect.

Future research should prioritize adequately powered randomized trials with standardized suicidal-ideation outcomes and assessment timepoints, direct comparisons of administration routes where clinically appropriate, and longer follow-up to determine the durability of early symptomatic improvement. Greater representation of adolescents and other understudied populations is also needed. Further studies examining the temporal relationship between suicidal ideation and depressive symptoms may help clarify whether these outcomes follow distinct or overlapping treatment-response trajectories.

Author contributions

Tariq H. Alotaibi: conceptualization, methodology, investigation, writing – original draft, project administration; Mazhar Mushtaq: writing – review and editing, software, visualization, validation; Abdulrahman Abdullah Altuwaim: investigation, data curation, writing – review and diting; Nawal Alammari: conceptualization, methodology, supervision, writing – review and editing, project administration; Fay Abdullah Almutairi: investigation, data curation, writing – review and editing; Saleh Ahmed Alzahrani: investigation, data curation, writing – review and editing; Ahmed Mohammed Alghamdi: investigation, data curation, writing – review and editing; Mariam Saleh M. Moshref: investigation, data curation, writing – review and editing; Mohammed Adel Alrehaili: investigation, data curation, writing – review and editing; Turki Falah M. Alrashidi: investigation, data curation, writing – review and editing; Nouf Mohammed Asiri: investigation, data curation, writing – review and editing; Ahmed Y. Azzam: conceptualization, methodology, formal analysis, software, visualization, validation, writing – original draft, supervision.

Use of AI tools declaration

The authors used a range of digital and AI-assisted tools at different stages of manuscript preparation and data management. These included ChatGPT (OpenAI), which was used to improve language clarity, structure, and academic wording. We also used software such as SPSS, Microsoft Excel, and Microsoft Office for data analysis, organization, formatting, visualization, and overall document preparation. Despite this support, the authors carefully reviewed and handled all aspects of the study, including interpreting findings, selecting studies, verifying data, making analytical decisions, and drawing final conclusions. The authors take full responsibility for the accuracy, originality, and integrity of the work presented.

Ethics approval and consent to participate

This study is a systematic review and meta-analysis of previously published studies; therefore, ethical approval from an Institutional Review Board (IRB) was not required. This study did not involve direct human participants as it exclusively analyzed data from previously published studies.

Conflict of interest

The author declares no conflict of interest.

References

1. Naghavi M (2019) Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the Global Burden of Disease Study 2016. *BMJ* 364: l94. https://doi.org/10.1136/bmj.l94
2. Yan N, Luo Y, Mackay LE, et al. (2024) Global patterns and trends of suicide mortality and years of life lost among adolescents and young adults from 1990 to 2021: a systematic analysis for the Global Burden of Disease Study 2021. *Epidemiol Psychiatr Sci* 33: e52. https://doi.org/10.1017/s2045796024000532

3. Pompili M (2024) On mental pain and suicide risk in modern psychiatry. *Ann Gen Psychiatry* 23: 6. https://doi.org/10.1186/s12991-024-00490-5
4. Gerhard DM, Duman RS (2018) Rapid-acting antidepressants: mechanistic insights and future directions. *Curr Behav Neurosci Rep* 5: 36–47.
5. Witkin JM, Martin AE, Golani LK, et al. (2019) Rapid-acting antidepressants. *Adv Pharmacol* 86: 47–96. https://doi.org/10.1016/bs.apha.2019.03.002
6. Lullau APM, Haga EMW, Ronold EH, et al. (2023) Antidepressant mechanisms of ketamine: a review of actions with relevance to treatment-resistance and neuroprogression. *Front Neurosci* 17: 1223145. https://doi.org/10.3389/fnins.2023.1223145
7. Ballard ED, Neely L, Waldman L, et al. (2025) Clinical indicators of the suicide crisis and response to ketamine. *J Affect Disord* 372: 126–133. https://doi.org/10.1016/j.jad.2024.11.080
8. Reif A, Bitter I, Buyze J, et al. (2023) Esketamine nasal spray versus quetiapine for treatment-resistant depression. *N Engl J Med* 389: 1298–1309. https://doi.org/10.1056/NEJMoa2304145
9. Rodolico A, Cutrufelli P, Di Francesco A, et al. (2024) Efficacy and safety of ketamine and esketamine for unipolar and bipolar depression: an overview of systematic reviews with meta-analysis. *Front Psychiatry* 15: 1325399. https://doi.org/10.3389/fpsyt.2024.1325399
10. Fountoulakis KN, Saitis A, Schatzberg AF (2025) Esketamine treatment for depression in adults: a PRISMA systematic review and meta-analysis. *Am J Psychiatry* 182: 259–275. https://doi.org/10.1176/appi.ajp.20240515
11. Jollant F, Colle R, Nguyen TML, et al. (2023) Ketamine and esketamine in suicidal thoughts and behaviors: a systematic review. *Ther Adv Psychopharmacol* 13: 20451253231151327. https://doi.org/10.1177/20451253231151327
12. Yavi M, Lee H, Henter ID, et al. (2022) Ketamine treatment for depression: a review. *Discov Ment Health* 2: 9. https://doi.org/10.1007/s44192-022-00012-3
13. Kang MJY, Hawken E, Vazquez GH (2022) The mechanisms behind rapid antidepressant effects of ketamine: a systematic review with a focus on molecular neuroplasticity. *Front Psychiatry* 13: 860882. https://doi.org/10.3389/fpsyt.2022.860882
14. Jóźwiak-Bębenista M, Sokołowska P, Wiktorowska-Owczarek A, et al. (2024) Ketamine—a new antidepressant drug with anti-inflammatory properties. *J Pharmacol Exp Ther* 388: 134–144. https://doi.org/10.1124/jpet.123.001823
15. Peiris ET, Pokhrel A, Paudel Y (2025) Ketamine for unipolar depression: a systematic review of efficacy and safety. *Australas Psychiatry* 33: 376–388. https://doi.org/10.1177/10398562251328805
16. Wang YT, Wang XL, Lei L, et al. (2024) A systematic review and meta-analysis of the efficacy of ketamine and esketamine on suicidal ideation in treatment-resistant depression. *Eur J Clin Pharmacol* 80: 287–296. https://doi.org/10.1007/s00228-023-03605-1
17. Sokołowska P, Seweryn Karbownik M, Jóźwiak-Bębenista M, et al. (2023) Antidepressant mechanisms of ketamine's action: NF-κB in the spotlight. *Biochem Pharmacol* 218: 115918. https://doi.org/10.1016/j.bcp.2023.115918
18. Page MJ, McKenzie JE, Bossuyt PM, et al. (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Rev Esp Cardiol* 74: 790–799. https://doi.org/10.1016/j.rec.2021.07.010

19. Seraj A, Reyazuddin M, Gaur RK, et al. (2025) Oral ketamine for rapid reduction of suicidal ideation in major depressive disorder: a midazolam-controlled randomized clinical trial. *Asian J Psychiatr* 106: 104413. https://doi.org/10.1016/j.ajp.2025.104413
20. Zhou Y, Lan X, Wang C, et al. (2024) Effect of repeated intravenous esketamine on adolescents with major depressive disorder and suicidal ideation: a randomized active-placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 63: 507–518. https://doi.org/10.1016/j.jaac.2023.05.031
21. Hochschild A, Keilp JG, Madden SP, et al. (2022) Ketamine vs midazolam: mood improvement reduces suicidal ideation in depression. *J Affect Disord* 300: 10–16. https://doi.org/10.1016/j.jad.2021.12.055
22. Gaither R, Ranney M, Peachey A, et al. (2022) A feasibility study of low-dose ketamine for acute management of suicidal ideation. *J Am Coll Emerg Physicians Open* 3: e12790. https://doi.org/10.1002/emp2.12790
23. Abbar M, Demattei C, El-Hage W, et al. (2022) Ketamine for the acute treatment of severe suicidal ideation: double blind, randomised placebo controlled trial. *BMJ* 376: e067194. https://doi.org/10.1136/bmj-2021-067194
24. Ionescu DF, Fu DJ, Qiu X, et al. (2021) Esketamine nasal spray for rapid reduction of depressive symptoms in patients with major depressive disorder who have active suicide ideation with intent: results of a phase 3, double-blind, randomized study (ASPIRE II). *Int J Neuropsychoph* 24: 22–31. https://doi.org/10.1093/ijnp/pyaa068
25. Domany Y, McCullumsmith CB (2022) Single, fixed-dose intranasal ketamine for alleviation of acute suicidal ideation. An emergency department, trans-diagnostic approach: a randomized, double-blind, placebo-controlled, proof-of-concept trial. *Arch Suicide Res* 26: 1250–1265. https://doi.org/10.1080/13811118.2021.1878078
26. Pathak U, Ahuja SK, Dwivedi R, et al. (2021) Antisuicidal efficacy of ketamine infusion in suicidal patients of depressive disorder. *Indian J Psychiatry* 63: 483–489. https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_80_21
27. Canuso CM, Ionescu DF, Li X, et al. (2021) Esketamine nasal spray for the rapid reduction of depressive symptoms in major depressive disorder with acute suicidal ideation or behavior. *J Clin Psychopharmacol* 41: 516–524. https://doi.org/10.1097/jcp.0000000000001465
28. Fu DJ, Ionescu DF, Li X, et al. (2020) Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: double-blind, randomized study (ASPIRE I). *J Clin Psychiatry* 81: 19m13191. https://doi.org/10.4088/JCP.19m13191
29. Domany Y, Shelton RC, McCullumsmith CB (2020) Ketamine for acute suicidal ideation. An emergency department intervention: A randomized, double-blind, placebo-controlled, proof-of-concept trial. *Depress Anxiety* 37: 224–233. https://doi.org/10.1002/da.22975
30. Grunebaum MF, Galfalvy HC, Choo TH, et al. (2018) Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. *Am J Psychiatry* 175: 327–335. https://doi.org/10.1176/appi.ajp.2017.17060647
31. Canuso CM, Singh JB, Fedgchin M, et al. (2018) Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 175: 620–630. https://doi.org/10.1176/appi.ajp.2018.17060720

32. Burger J, Capobianco M, Lovern R, et al. (2016) A double-blinded, randomized, placebo-controlled sub-dissociative dose ketamine pilot study in the treatment of acute depression and suicidality in a military emergency department setting. *Mil Med* 181: 1195–1199. https://doi.org/10.7205/milmed-d-15-00431
33. Murrough JW, Soleimani L, DeWilde KE, et al. (2015) Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychol Med* 45: 3571–3580. https://doi.org/10.1017/s0033291715001506
34. Chammas F, Januel D, Bouaziz N (2022) Inpatient suicide in psychiatric settings: evaluation of current prevention measures. *Front Psychiatry* 13: 997974. https://doi.org/10.3389/fpsyt.2022.997974
35. Seyedoshohadaei SA, Darehbagh RR, Gholami F, et al. (2024) Ketamine's efficacy in alleviating acute suicidal thoughts: a comprehensive systematic review and meta-analysis. *Middle East Curr Psy* 31. https://doi.org/10.1186/s43045-024-00428-3
36. Bahji A, Vazquez GH, Zarate CA Jr (2021) Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. *J Affect Disord* 278: 542–555. https://doi.org/10.1016/j.jad.2020.09.071
37. Zanos P, Gould TD (2018) Mechanisms of ketamine action as antidepressant. *Mol Psychiatr* 23: 801–811. https://doi.org/10.1038/mp.2017.255
38. Hochschild A, Grunebaum MF, Mann JJ (2021) The rapid anti-suicidal ideation effect of ketamine: a systematic review. *Prev Med* 152: 106524. https://doi.org/10.1016/j.ypmed.2021.106524
39. Witt K, Potts J, Hubers A, et al. (2020) Ketamine for suicidal ideation in adults with psychiatric disorders: a systematic review and meta-analysis of treatment trials. *Aust N Z J Psychiatry* 54: 29–45. https://doi.org/10.1177/0004867419883341
40. Kosik-Gonzalez C, Fu DJ, Chen LN, et al. (2025) Effect of esketamine on depressive symptoms in adolescents with major depressive disorder at imminent suicide risk: a randomized psychoactive-controlled study. *J Am Acad Child Psy* 65: 42–55 https://doi.org/10.1016/j.jaac.2025.02.015

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